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CONTENTS OF PREVIOUS NUMBER

AUGUST 1948. NUMBER 2

Necrosis of Intraocular Tissues. Bernard Samuels, M.D., New York.

Incidence of Defective Color Vision Among Psychotic Patients. LeGrand H. Hardy, M.D.; Gertrude Rand, Ph.D., and M. Catherine Rittler, A.B., New York.

Preplacement of Air in Cyclodialysis. Sol Rome, M.D., and Raphael Koff, M.D., Los Angeles.

Deep Keratitis Associated with Atypical Lichen Planus: Report of a Case. J. Goldsmith, M.D., New York.

An Aid in Detecting Trachoma-Like Inclusion Bodies in the Conjunctiva. Martin Bodian, M.D., Brooklyn.

Occlusion of the Cilioretinal Artery. Jesse M. Levitt, M.D., Brooklyn, N. Y.

"Silent" Dacryocystitis. Frederick H. Theodore, M.D., New York.

The History of the Dartmouth Eye Institute. Hermann M. Burian, M.D., Boston.

Di-Isopropyl Fluorophosphate (D F P) in Treatment of Glaucoma: Further Observations. Irving H. Leopold, M.D., and P. Robb McDonald, M.D., Philadelphia.

Lattice Type of Hereditary Corneal Degeneration: Report of Five Cases, Including One of a Child of Two Years. Frederick C. Stansbury, M.D., Syracuse, N. Y.

Abstracts from Current Literature.

Obituaries:

H. Maxwell Langdon, M.D.

Book Reviews.

ARCHIVES OF OPHTHALMOLOGY

VOLUME 40 (OLD SERIES VOLUME 97) SEPTEMBER 1948 NUMBER 3

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SUCCESSFUL DIATHERMY TREATMENT OF RECURRING RETINAL HEMORRHAGE AND RETINITIS PROLIFERANS

Report of a Case

F. H. VERHOEFF, M.D.
BOSTON

RECURRING RETINAL hemorrhage in young persons is frequently associated with ophthalmoscopically recognizable periphlebitis. In most cases the patient gives a cutaneous reaction to tuberculin, and in the cases in which the retina has been examined microscopically nodular foci of epithelial cells have been observed along the veins. These facts constitute strong evidence that the condition termed by Igersheimer "periphlebitis adolescentium" is an entity, that it is caused by tuberculosis and that to it most cases of so-called Eales's disease belong. It is uncertain whether the periphlebitis is directly hematogenous or results from dissemination of the infection by way of the vitreous. Microscopically, I have seen such foci along retinal veins in the vicinity of localized active foci of tuberculous chorioretinitis, and there they were obviously due to migration of infected macrophages within the vitreous. The hemorrhages evidently result from engorgement of capillaries and small veins. When this engorgement is severe and persistent, new vessels are formed, which may extend into the vitreous. At the same time, hemorrhage into the vitreous usually occurs, and the extravasated blood becomes organized by the new vessels, thus producing typical retinitis proliferans. Periphlebitis is not certainly the immediate cause of the capillary engorgement and hemorrhages, for in some cases, including those of retinitis proliferans, it is not visible, and even in cases in which it is conspicuous it is often not so situated as to explain the hemorrhages. It would seem, therefore, that the vascular lesions causing the hemorrhages are usually too small to be visible with the ophthalmoscope.

For this condition, treatment heretofore used, including injections of tuberculin, has been of doubtful value. So far as I know, the present case is the only instance of recurring hemorrhages in which diathermy treatment has been employed.

Read at the Eighty-Third Annual Meeting of the American Ophthalmological Society, Hot Spring, Va., June 6, 1947.

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REPORT OF CASE

History.—H. T. H. was first seen by me on Aug. 10, 1939, when he was 18 years of age. With a correction of —0.37 cyl., axis 180 for the right eye and of —0.37 cyl., axis 165 for the left eye, vision was 20/15— in each eye. There was 3Δ of exophoria. The fundi, pupils and visual fields were normal. Glasses were not ordered.

On May 25, 1943 the patient entered naval service as ensign, and about April 15, 1944, while on submarine duty, he noticed blurred vision in the right eye. This cleared up but recurred five weeks later, so that ever afterward he had to use the left eye for periscopic observations. He was sent to a naval hospital on July 11,[1] where, on September 8, vision in the right eye was observed to have cleared to 20/40. Shortely after this, while he was at home on leave, vision in the right eye was reduced to light perception, but on October 28 it had cleared to 6/20. On December 4 vision again failed in the right eye and has never since been better than ability to count fingers at 2 feet (60 cm.).

The Naval medical service in 1944 made a diagnosis of hemorrhage into the vitreous and retinitis proliferans in the right eye. General physical examination, including a roentgenographic study of the chest and paranasal sinuses, revealed nothing remarkable. Agglutination tests gave negative reactions for typhoid the paratyphoid bacilli, Proteus vulgaris 0X19 and Brucella abortus. The cutaneous reaction to tuberculin was positive. A later test, made on Feb. 15, 1945, with a dilution of 1:100,000, gave a 3 plus reaction.

For two months the patient was given, without benefit, biweekly or weekly injections of old tuberculin U.S.P. He was also given potassium iodide; later, large doses of ascorbic acid, and, finally, injections of penicillin. These substances were believed to have been of some benefit but did not completely check the process, and on Jan. 3, 1945 hemorrhages were noted in the left eye. With regard to this finding, Comdr. Raymond E. Meek wrote me from the United States Naval Hospital, Newport, R. I.: "At present the left eye has vision of 20/20, but above and temporal to the macula are small droplets of blood hanging down into the vitreous, and strands of what appears to be exudate coming away from the retina, with new vessels growing into it." The patient was discharged from the Navy on May 1, 1945.

Ophthalmic Examinations.—The patient had consulted me on Sept. 6, 1944, while still in naval service. The right eye showed two foci of retinitis proliferans, one a short distance nasal to, and the other below, the optic disk. Between the disk and the macula were a number of small exudates, such as occur in circinate retinitis (lipid deposits). The inferior temporal vein was sheathed in white for a considerable distance. There were a number of hemorrhages in the retina and a gray mass of old blood in the viterous below. Vision in the right eye was 20/40. The left eye was normal; its visual acuity was 20/15—.

Feb. 13, 1945: The patient again consulted me. The vitreous of the right eye was full of blood. The left eye showed retinal hemorrhages in the upper outer quadrant, but its visual acuity was still 20/15—.

February 24: The patient came to Boston on terminal leave and placed himself under my care. Treatment with "diasone" (the disodium formaldehyde

1. While the patient was in the hospital, an ammunition depot 2 miles (32 kilometers) away blew up. The patient left the hospital without permission and assisted in extinguishing the fire in several cars loaded with ammunition. For this he was awarded the Navy Marine Corps Medal.

sulfoxylate derivative of diaminodiphenylsulfone) was begun, and the patient was instructed to see me weekly.

March 10: Morning temperatures taken recently had ranged from 96.7 to 97 F.

April 14: There were definite retinitis proliferans in the upper outer quadrant of the left eye and fairly large retinal hemorrhages still farther out.

April 28: The vessels extended farther into the vitreous of the left eye. In the crotch between the two branches of a retinal vein near the area of retinitis proliferans was a round white spot (periphlebitis) about 1/3 disk diameter in size, and next to this, a smaller white spot. The new tissue in the vitreous had increased. Vision in the left eye was 20/15—. The treatment with "diasone" was discontinued, and diathermy was decided on.

May 8: A canthotomy was performed on the left eye. The sclera was exposed in the upper outer quadrant. Several weak and three strong applications of surface diathermy were made over the affected region of the retina. Ophthalmoscopic examination then showed extensive white areas in this region. There was no hemorrhage into the vitreous.

May 15: Small hemorrhages were seen in the white areas.

May 22: The white areas were turning gray and showed pigmentation around them. Vision in the left eye was 20/15—. Potassium arsenite solution U.S.P. was prescribed.

October 8: The treated areas were atrophic and pigmented. Delicate tissue (old retinitis proliferans) still extended into the vitreous but was free of visible vessels. There were no retinal hemorrhages.

Feb. 13, 1946: This morning the patient had noticed some disturbance in the upper outer quadrant of the visual field of the left eye. Several fresh retinal hemorrhages were seen at, and anterior to, the equator of the eye, in the lower inner quadrant. Vision was 20/15—. Diathermy was decided on.

February 15: The retinal hemorrhages had increased in number and now involved the region from 2 to 5 o'clock. At operation, the sclera was exposed below and the tendon of the inferior rectus cut. Numerous nonperforating diathermy points (0.5 mm.) were applied in the region of the hemorrhages. Ophthalmoscopic examination then showed the treated areas to be almost continuous.

February 16: There were many new hemorrhages above the treated region. Some were near the fovea.

February 27: The patient was discharged from the hospital.

March 2: The retinal hemorrhages had mostly disappeared. A small streak of blood, which may previously have been overlooked, extended into the vitreous from below. The vitreous was filled with fine, dustlike opacities. Vision in the left eye was 20/20— with a correction of —0.50 sph. —0.75 cyl., axis 190.

May 6: The right eye diverged. The fundus was not visible. Vision was limited to perception of hand movements in this eye. Numerous nonperforating diathermy points were applied in the lower half of the eye.

May 13: The upper half of the right eye was treated in the same way as the lower half.

May 5, 1947: Right eye: The fundus was still invisible. Tension was normal. Vision was limited to counting fingers at 1 foot (30 cm.). Left eye: There have been no new hemorrhages. The treated areas were atrophic and pigmented. The visual field (figure) indicates their location. Vision was 20/30— without correction and 20/15— with a correction of —0.25 sph. —0.75 cyl., axis 165.

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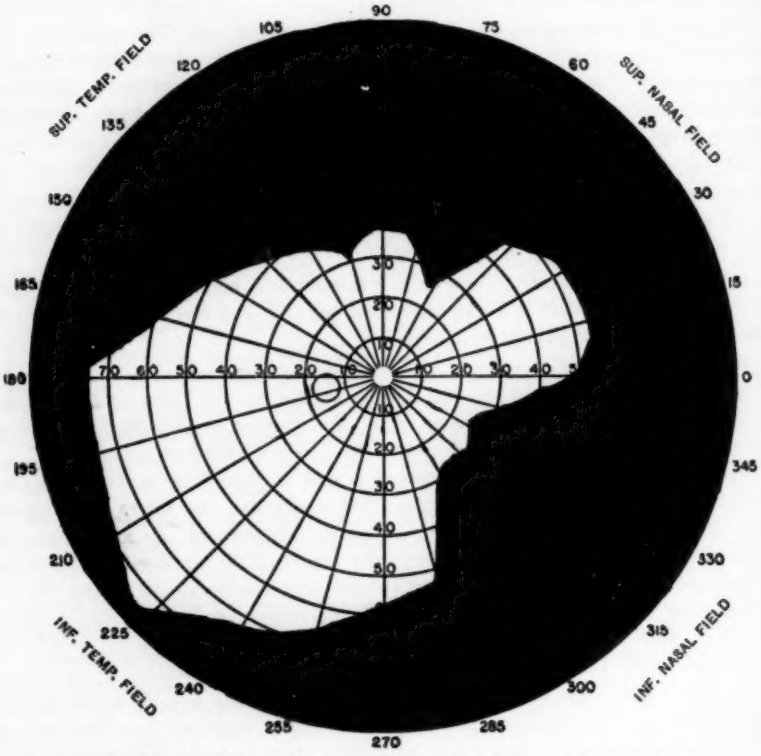
COMMENT

When this patient came under my care, vision seemed to be hopelessly lost in the right eye, and retinitis proliferans indicated the same fate for the left eye. "Diasone" had been sent me for trial in cases of ocular tuberculosis, and I therefore tried it with this patient. No improvement having occurred in two months, this treatment was abandoned. It then occurred to me that diathermy treatment, such as is used for deatchment of the retina, might check the process in the left eye and, at the same time, fasten down the retina so that it could not be pulled off as a result of



Contraction of the visual field of the left eye produced by diathermy.

the retinitis proliferans. Presumably, this treatment would destroy the inflammatory foci, whether tuberculous or not, and thus prevent dissemination of infection from them. It would also obliterate the vessels from which the hemorrhages arose. Accordingly, surface diathermy was applied to the affected region in the left eye. When the reaction had subsided, the treated areas presented an appearance similar to that after successful diathermy treatment of detached retina. The foci of periphlebitis had been destroyed, and the hemorrhages had disappeared. Deli-

cate tissue resulting from the previous retinitis proliferans still projected into the vitreous, but it was free from visible vessels. Beneath it, the retina was fused with the choroid and hence was no longer in danger of being pulled off. Visual acuity with glass was 20/15—.

The condition of the left eye remained unchanged until nine months later, when the patient noticed slight visual disturbance, although his visual acuity was still 20/15—. I found a number of large retinal hemorrhages at the periphery of the retina in the lower inner quadrant. In the course of two days the region from about 8 to 5 o'clock was covered with hemorrhages. No periphlebitis was recognizable. Since these hemorrhages were remote from the previously treated retinal area, it is probable that they were due to fresh hematogenous infection. The entire hemorrhagic region was then subjected to diathermy, as described. Numerous additional hemorrhages produced by this treatment seemed alarming at the time, but all the blood had disappeared at the end of about three weeks. Up to time of this report, fifteen months after the second episode, there has been no recurrence of hemorrhage in the left eye.

As a result of the treatments, the visual field is, of course, considerably constricted, but the patient is not aware of any handicap from this source. There has also been produced a slight amount of myopia and an increase in myopic astigmatism. Whereas before the treatments the visual acuity of the left eye was 20/15—, a glass is now required to obtain this vision, and without glass the visual acuity is only 20/30—.

Although vision in the right eye seemed to be hopelessly lost, numerous applications of diathermy were made around the entire equator of this eye, after it had become apparent that the treatment of the left eye was successful. Persisting cloudiness of the vitreous still makes it impossible to determine whether this treatment has been of benefit. Probably useful vision could have been saved in this eye if the diathermy had been used while the vitreous was still clear and central vision was fairly good.

It is probable that the patient has now passed through the period of liability to recurrence of hemorrhages. If, however, retinal hemorrhages again occur in the left eye, I shall treat the affected areas with diathermy to the extent to which I can do so without endangering central vision.

There is still another way in which diathermy may possibly be of benefit, not only in selected cases of tuberculous periphlebitis but in cases of retinal vascular obstruction from any cause. It may establish communication between retinal and choroidal vessels and thus restore retinal circulation. The appearances I noted in some of the treated areas in the present case strongly indicated that such a communication had been made. It would seem, therefore, that attempts to establish by this or other means such collateral circulation should be made in all cases of impending blindness from obstruction of retinal vessels. These cases would in-

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clude those of partial obstruction of the central vein or artery, cases of pronounced sclerosis of the retinal vessels with impending impairment of central vision and early cases of circinate retinitis. In cases of complete obstruction of the central vein the treatment might at least prevent the development of hemorrhagic glaucoma. It might even offer some hope in cases of diabetic retinopathy.

The possible establishment of a collateral circulation also offers hope in cases of retinitis proliferans arising from the disk or its vicinity. Here, of course, the affected vessels cannot safely be obliterated by diathermy, but establishment of a collateral circulation near the disk might relieve the venous congestion and thus check the proliferation of new vessels.

395 Commonwealth Avenue.

DISCUSSION

Dr. Arthur J. Bedell, Albany, N. Y.: I shall show several photographs in the latest case of angiomatosis in which I have operated. The first, taken three months before the last, shows immense dilatation of the superior temporal artery and vein, exudate in and about the macular region and, far to the temporal side, the well demarcated angioma, with fine capillaries on its surface. After multiple diathermy punctures, the exudate was less and the angioma flatter, with dark but not black scars, representing much less destruction than that after a strong diathermy current.

With regard to diathermy, I suggest a word of warning, for two reasons: First, it is impossible accurately to control the delivered current in a great group of vessels, and, second, many changes ascribed to the treatment may be those which would have occurred had nature not been interfered with. The procedure should be tried on animals before it is recommended for use on human subjects.

Dr. Ralph C. Rychener, Memphis, Tenn.: I was interested in Dr. Verhoeff's suggestion that his procedure be used for certain vascular obstructions, particularly obstruction of the central vein. Does Dr. Verhoeff think that in a case of complete obstruction of the central vein such an attempt would be worth while?

Dr. F. H. Verhoeff, Boston: The suggestion of using diathermy in cases of obstruction of the central vein is based on theoretic considerations. The possibility of establishing communications between the choroid and the retinal circulation is something that should be worked on experimentally. The outlook in these cases is so hopeless that it is justifiable to carry out the experiments on human subjects. If visual acuity is already practically abolished, no return is to be expected; but if one could get the retinal circulation established secondary glaucoma might be prevented. Experimental investigation should be carried out to determine whether much, or only a little, heat should be applied. I should do the experiments on dogs, not rabbits. With such a wonderful circulation as exists in the choroid, it seems too bad not to utilize it when the circulation in the retina is lost.

OCULAR CHANGES ASSOCIATED WITH SCRUB TYPHUS

A Study of Four Hundred and Fifty-One Patients

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VARIOUS OCULAR changes associated with scrub typhus (mite-borne typhus tsutsugamushi fever) were described by me in reports submitted to the Office of the Surgeon General of the United States army in 1944 and 1945. Abstracts of these reports were released in the *Bulletin of the United States Army Medical Department* in April 1945[1] and April 1946.[2] The external ocular changes consisted of conjunctival injection, occurring during the onset of the disease, and occasionally, subconjunctival hemorrhages, appearing during the first ten days. The intraocular changes, previously undescribed, were more noteworthy. The commonest, and most striking, of these was edema of the disk and retina, occurring during the second and third weeks of the disease and persisting well into convalescence. Retinal hemorrhages, usually superficial in type, and white, soft exudates occurred in a smaller number of patients. When these did occur, they were usually associated with edema of the disk and retina.

Subsequent to my original report, Macaskill,[3] in October 1945; Dame,[4] in November 1945, and Donegan,[5] in January 1946, reported ocular changes occurring with scrub typhus. Macaskill studied 70 pa-

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Submitted as a candidate's thesis in partial fulfilment of the requirements for membership in the American Ophthalmological Society, 1947.

*Formerly Major, Medical Corps, Army of the United States.

1. Scheie, H. G.: Ocular Changes in Scrub Typhus, Bull. U. S. Army M. Dept., April 1945, no. 87 p. 37.

2. Scheie, H. G.: Ocular Changes in Scrub Typhus, Bull. U. S. Army M. Dept. **5**:423 (April) 1946.

3. Macaskill, J.: Some Ocular Complications of Scrub Typhus, Brit. J. Ophth. **29**:537, 1945.

4. Dame, L. R.: Eye and Ear Sequelae of Scrub Typhus Fever, Bull. U. S. Army M. Dept. **4**:554 (Nov.) 1945.

5. Donegan, E. A.: Ocular Findings in Tropical Typhus, Brit. J. Ophth. **30**:11 (Jan.) 1946.

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tients. He found subconjunctival hemorrhages in 4 patients, intense engorgement of the retinal veins in 7 patients, papilledema in 4 patients, retinal hemorrhages in 1 patient and bilateral atrophy of the optic nerve in 1 patient, seen six months after the acute stage of the illness. No pathologic studies were made. Dame examined 50 patients during convalescence. He found nonspecific hyperemia of the optic disks. No other retinal changes were noted. He observed greatly enlarged blindspots in most of the eyes and contraction of the visual fields in some, the amount averaging 15 degrees. Ten eyes showed scotomas. No permanent loss of

Fig. 1.—Typical primary lesion, containing an eschar. Army Institute of Pathology, Washington, D. C.

visual acuity was noted. Donegan observed 101 patients. He reported on 32 patients showing haze of the vitreous. Seventeen of his patients had papilledema, which he interpreted as due to vascular disturbance, and not true neuritis. Other patients showed blurring of the disks, not interpreted as papilledema.

The present study describes, in some detail, the ocular changes observed in the routine examination of 451 patients with scrub typhus. Pathologic studies were carried out on eyes removed at autopsy from 9 of these patients. An attempt will be made to correlate the ophthalmologic and the general clinical findings.

CLINICAL PICTURE

Scrub typhus is an acute febrile illness caused, as demonstrated by Lewthwaite and his associates,[6] by Rickettsia ripponica. The rickettsia is transmitted by the larval form of a mite, Trombicula akamushi, family Trombidiidae, order Acarina. The disease is endemic in China, India, Burma, the Federated Malay States, Indo-China, Japan, Netherland East Indies, New Guinea, the Solomon Islands and North Queensland. A

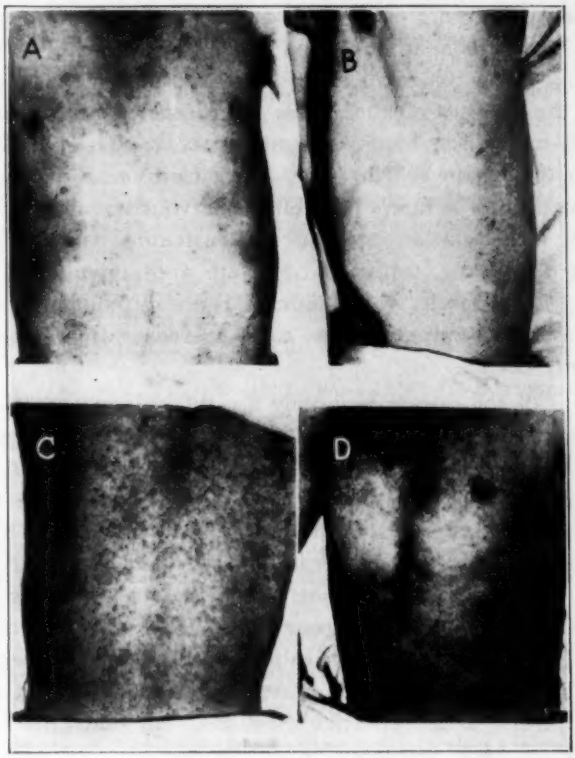

Fig. 2.—Appearance of the rash of scrub typhus. *A*, sparse maculopapular rash on the fifth febrile day; *B*, fine, discrete rash, largely macular, on the sixth day of fever; *C*, well developed maculopapular rash on the eighth febrile day; *D*, blotchy, coarse maculopapular rash on the tenth day of fever (after Sayen and others[8]).

papule develops at the site of the mite bite and usually progresses to formation of an ulcer, 5 to 7 mm. in diameter, characteristically containing a black eschar (fig. 1). The eschar was seen in 60 per cent of the the series. It can occur anywhere on the body. The incubation period is estimated to be from ten to nineteen days, followed by relatively abrupt onset of the disease. The onset is characterized by chilliness, fever, malaise, headache and generalized aching. The elevation of temperature increases

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during the first week of the disease, until in most instances it reaches 103 to 105 F. Wide daily fluctuations in the temperature are characteristic. The fever usually subsides by lysis during the third week of the disease.

A rash, which is macular or maculopapular in type and involves the trunk, and sometimes the face and extremities, appears in most patients from the third to the sixth day of the disease (fig. 2). It lasts from three to five days. Ninety to 95 per cent of the patients in the present series showed generalized lymphadenopathy. Regional adenopathy is usually present with appearance of the eschar. Splenomegaly occurred in 34 per cent. The patient is apathetic. Conjunctival injection is common. Early in the disease many patients have a cough and the physical signs of bronchitis. As the severity of the illness increases, typhus pneumonia may occur, with tachypnea, hyperpnea and cyanosis. The blood pressure is usually low during the febrile stage. Myocarditis may develop, but congestive heart failure is rare. The central nervous system is frequently affected. The manifestations are muscular twitching, paresthesia, transient diminution of hearing, confusion, delirium and convulsions. Nystagmus occurs much more rarely. Renal damage is not infrequent in severe cases. The fever usually terminates in two to three weeks, after which prolonged convalescence occurs.

Diagnosis of the disease is usually not difficult in endemic areas, especially when the eschar, lymphadenopathy and rash are present. The Weil-Felix test is an important confirmatory means. A significant agglutination titer against Proteus vulgaris O X K is found in a majority of patients, while an insignificant titer is obtained against the O X 2 and O X 19 strains. The positive reaction is usually obtained during the third week of the disease. The mortality in the armed forces has ranged from 2 to 10 per cent. The prognosis is best in young persons who have previously been in good general health and who can be given early hospital care. No specific treatment is available, the therapeutic steps being rest, good nursing and supportive measures. No protective vaccine for man has as yet been developed. Clothing impregnated with dimethylphthalate and dibutylphthalate is protective. The mites are most prevalent in areas of scrub jungle overgrowth, particularly along rivers subject to floods. Lying or sleeping on the ground in such places should be avoided.

SOURCE OF MATERIAL

The ophthalmologic studies reported here, all made by me in the capacity of chief of the ophthalmologic section, were part of a general clinical study of the disease carried out by the medical service of the Twentieth General Hospital from October 1943 to February 1945. A total of 616 cases were made available. All

6. Lewthwaite, R., and Savoor, S. R.: Typhus Group of Diseases in Malay, Brit. J. Exper. Path. **17**:1 (Feb.); 461 (Dec.) 1936.

the patients had contracted the disease in Assam and Burma, where scrub typhus, hitherto unsuspected, became manifest during the North Burma campaign of 1943 to 1945. The results of this work have been reported by Machella and Forrester[7] and Sayen, Pond, Forrester and Wood.[8] Most of the statistics cited here were obtained from a series of 200 consecutive patients studied in detail by Sayen and associates.[8] Adequate ophthalmologic data were recorded on 451 of the 616 patients. The data correlating the ocular and the general clinical findings were derived from studies on 159 of the 200 patients just mentioned.

METHOD OF OPHTHALMOLOGIC STUDY

The first patients who were admitted to the Twentieth General Hospital with scrub typhus presented a perplexing diagnostic problem. The personnel were unfamiliar with this disease and were further misled by the fact that scrub typhus had not previously been reported from the area of India and Burma in which we were stationed. In consequence, numerous diagnostic tests and consultations were carried out, including an ophthalmologic study. The eyegrounds of these first patients were examined at least twice weekly, in the hope of finding some bit of evidence that might be of diagnostic value. This undoubtedly led to the discovery of the lesions in the fundus, since they develop late in the disease, with onset during the second and third weeks.

Unusual ocular changes were seen to develop in a rather large number of patients. Therefore, when the disease was recognized and greater numbers of these patients were admitted to the hospital, ocular examinations were carried out routinely. Every patient admitted to the hospital who was suspected of having scrub typhus was subjected to ophthalmic examinations once a week or oftener, with the pupils dilated. Visual acuity was determined for all patients with Snellen type at a distance of 20 feet (6 meters) or with Jaeger type at reading distance, and the visual fields were taken for most of the patients with retinopathy as early as this could be done. Peripheral fields were determined on a perimeter having a radius of 330 mm. with a 1 mm. white test object, and central fields were plotted with the same test object on a tangent screen at 1 meter. Examinations with the slit lamp could be performed only during convalescence, when the patient was brought to the clinic. The observations are recorded under two headings: extraocular and intraocular.

ROUTINE OPHTHALMOLOGIC OBSERVATIONS

EXTRAOCULAR EXAMINATION (FIG. 3)

Conjunctival Injection.—Conjunctival hyperemia was prevalent during the early stages of the disease, usually with no discharge, and tended to disappear during the second and third weeks. During the second week, when we first saw some of the patients, the hyperemia may have subsided. Nevertheless, hyperemia was present in 174 patients (38.8 per cent of the entire series). Cultures of secretions from the conjunctiva

7. Machella, T. E., and Forrester, J. S.: Mite Typhus: Clinical and Laboratory Study of Sixty-Four Cases, Am. J. M. Sc. **210**:38 (July) 1945.

8. Sayer, J. J.; Pond, H. S.; Forrester, J. S., and Wood, F. C.: Scrub Typhus in Assam and Burma: Clinical Study of Six Hundred and Sixteen Cases, Medicine **25**:155 (May) 1946.

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showed no significant incidence of pathogenic organisms, and conjunctival scrapings were negative for inclusion bodies.

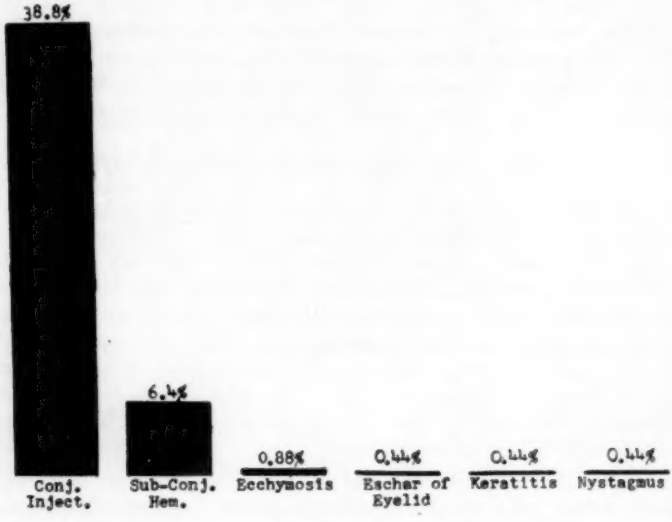

Fig. 3.—Incidence of extraocular changes. Army Institute of Pathology, Washington, D. C.

Fig. 4.—Bilateral subconjunctival hemorrhages. Army Institute of Pathology, Washington, D. C.

Subconjunctival Hemorrhages.—Bulbar subconjunctival hemorrhages, presenting a striking appearance, occurred in 29 patients (6.4 per cent) during the first ten days of the disease. In 18 they were bilateral and in

11 unilateral (fig. 4). As a rule, the hemorrhages were massive, at times covering one third to one half of the exposed sclera.

Ecchymosis of the Eyelids.—Ecchymosis of the eyelids was seen in 4 cases. This also occurred early in the disease.

Eschar of the Eyelids.—An eschar, typical of the primary lesion of the disease, the result of a mite bite, was seen involving the upper lid of 2 patients (fig. 5).

Keratitis.—Ulcerative keratitis occurred in only 2 patients. In both instances it was believed to be nonspecific and of the type due to corneal exposure in very sick patients.

Nystagmus.—In 2 patients an unusual type of nystagmus developed during the course of their disease. The nystagmus was manifested by coarse, irregular, jerky, incoordinate movements of the eyes from side to side while the patient attempted to fix on an object. The amplitude of

Fig. 5.—Primary lesion of the eyelid. Army Institute of Pathology, Washington, D. C.

the movements gradually diminished as fixation was accomplished. The eyes would then remain quiet until fixation on another object was attempted. The movement greatly resembled the type of incoordination seen in extremities associated with cerebellar lesions and could well be called "fixation" nystagmus.

OPHTHALMOSCOPIC EXAMINATION (FIG. 6)

Vascular Changes.—Engorgement of Veins: As in the original study, venous engorgement was the most consistent finding and always preceded the other intraocular changes. It occurred in 67.2 per cent of the entire series of 451 patients. The onset was noted during the first or second week of the disease. When the disease was progressive, venous engorgement increased, until not infrequently the veins were two to two and one-half times the diameter of the arteries. As venous engorgement progressed, the following vascular changes developed:

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(*a*) Irregularity in Caliber of Veins: The veins were noted to become irregular in caliber as the engorgement increased. This change was particularly noticeable in the region of the disk, especially along the inferior temporal veins. The veins frequently appeared sausage like, due to localized dilatation, this appearance being accentuated by increased tortuosity of the vessels.

(*b*) Blurring of Outlines of Veins: Accompanying the dilatation and irregularity of the veins was haziness of the outline of their walls, especially in the region of the disk. This was not due to a definite perivascu-

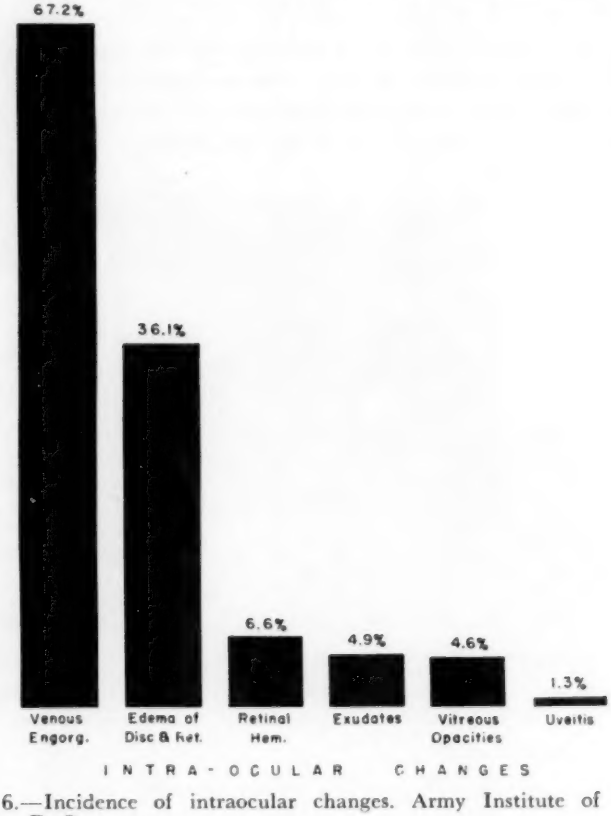

Fig. 6.—Incidence of intraocular changes. Army Institute of Pathology, Washington, D. C.

lar sheath, but appeared instead to be a veil-like phenomenon. Part of this appearance could no doubt be explained by retinal edema, with a somewhat blurred appearance of the entire posterior pole of the eye. Even though the arteries near the disk were often hazy, they never showed a degree of veiling comparable to that of the veins. For this reason, it was felt that fibrinous exudate was escaping from the vessels. Further support of this was given by the presence of occasional hemor-

rhages, which appeared to be in the outer coats of the veins, or adjacent to them along their walls.

(*c*) Thrombosis of Veins: Though thrombosis of the retinal veins appeared imminent in many cases, as judged by their extreme engorgement and their irregularity, it was observed only once in the entire series. The patient was unusually ill, and the course of his disease was protracted. The thrombosis was bilateral, involving the inferior temporal vein of his right eye and the inferior nasal vein of his left eye.

(*d*) Arteriovenous Crossing Phenomenon: As the venous engorgement became more pronounced, the veins appeared to be compressed, and frequently interrupted, at the arteriovenous crossings. The reason for this

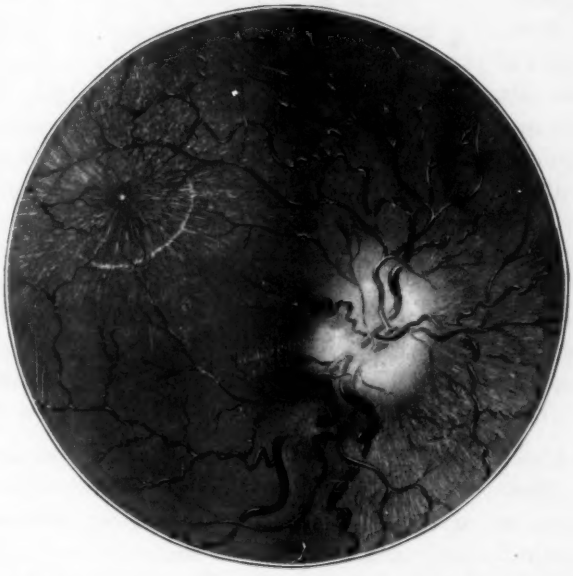

Fig. 7.—Drawing of the fundus, showing edema of the disk, venous engorgement and changes in arteriovenous crossings. Army Institute of Pathology, Washington, D. C.

is not clear. The compression could have been due to localized indentation of the distended venous wall by the more resistant wall of the artery. The interruption seemed to be caused by an exudation at the arteriovenous crossing, filmy in type, obscuring the venous wall adjacent to the artery.

(*e*) Arterial Changes: Changes in the retinal arteries appeared to be secondary to the other changes in the eyegrounds. The most remarkable of these was the exudation at the arteriovenous crossings, but this was a diffuse veil rather than a periarterial or a perivenous sheath. At times the arteries seemed pale, but this was difficult to evaluate. Near the

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margins of the disk the arteries were often obscured and seemed to show sheathing, but the entire area around the disk was affected to an equal, or a greater, degree.

Edema of the Disk and Retina.—Edema of the disk and retina (fig. 7) was seen in 163 of the 451 patients (36.1 per cent). It was the commonest manifestation of retinopathy. It was always preceded by engorgement of the retinal veins. It was always bilateral and both the disk and the retina were always involved, though to varying degrees. In some cases it resembled papilledema due to increased intracranial pressure, but the swelling was never very great, usually less than 1.5 D. and never over 2.5 D. Moreover, the posterior pole of the eye was diffusely edematous. The retinal edema and that of the disk were usually of about the same magnitude. Less often the retina showed pronounced edema and the disk almost none. The criteria for edema of the disk were definite elevation of the nerve head and blurring and obscuring of margins of the disk, most prominent at the nasal side and at the upper and lower poles. The presence of edema of the retina was established by the irregular light reflexes from the retina, the wavy, tortuous course of the veins and the translucent retinal folds running parallel to the temporal margins of the disk. In many cases these folds radiated from the macula also. The physiologic cups tended to be filled. The disk and the surrounding retina showed increased capillarity and a veiled, somewhat opaque, appearance. Edema of the disk and retina appeared during the second or third week of the disease. It persisted for one or two weeks and then began to subside slowly, often being apparent for several weeks after defervescence.

Retinal Hemorrhages.—Retinal hemorrhages were observed in 30 of the 451 patients (6.6 per cent). In 24 patients they were superficial (flame shaped or striate). Three patients had deep punctate hemorrhages in the macular region. Two others had preretinal hemorrhages. In the patient in whom thrombosis of the retinal veins developed, hemorrhages of all types were seen. The hemorrhages were unilateral in 25 patients, usually occurring singly at the posterior pole of the eye, not far from the disk. Except in 3 instances the hemorrhages were associated with edema of the disk and retina. They usually appeared at the time when the edema of the disk and the vascular changes were most marked.

Retinal Exudates.—Fluffy, white exudates were observed in 22 patients (4.9 per cent) of this series. They were usually of the cotton-wool variety; a few resembled ganglioform degeneration. They occurred singly in 19 patients and were multiple in 3. With 1 exception, the exudates were associated with edema of the disk and retina. They occurred at about the same time as the retinal hemorrhages and had the same distribution. They were associated with retinal hemorrhages in 9 eyes.

Uveitis and Opacities of the Vitreous.—Definite uveitis was seen in 6 patients (1.3 per cent). Opacities of the vitreous without cleancut evidence of uveitis were seen in 21 patients (4.6 per cent). The opacities were dustlike and most numerous in the posterior portion of the vitreous. The uveitis was remarkably asymptomatic except in 1 patient, in whom secondary glaucoma developed. Usually the only complaints were photophobia and slightly blurred vision. Ciliary injection was noted in only 2 of the 6 patients. All the patients with uveitis had keratic precipitates, a pronounced aqueous flare, and many floating clumps of cells, and 1 had Koeppe nodules. Of the 21 patients showing opacities of the vitreous without uveitis, 18 had retinal edema. The other 3 showed intense venous engorgement. Of the 6 patients with uveitis, 4 showed retinal edema.

ONSET AND DURATION OF RETINOPATHY

The appearance of retinopathy could usually be anticipated when venous engorgement became intense. However, the diagnosis was not made except on the basis of edema, hemorrhage or exudate. These manifestations occurred as early as the seventh day, but usually appeared from the tenth to the seventeenth day. The duration of the retinopathy varied considerably. The average time of disappearance was the eighth week of the disease. In some eyes it persisted as long as thirteen or fourteen weeks. No residual effect on visual function was detected, although in a small number of patients a mild pigmentary disturbance, possibly due to retinal atrophy, was seen adjacent to the macula.

VISUAL FUNCTION

Visual acuity was determined routinely. No definite evidence of visual defect was observed in any patient with retinopathy. The patients with uveitis sometimes complained of blurred vision. Occasionally there was slight enlargement of the blindspots.

DIFFERENTIAL DIAGNOSIS

The retinopathy of scrub typhus must be differentiated from papilledema and optic neuritis, as well as from the retinopathy of renal and hypertensive vascular disease. Papilledema due to increased intracranial pressure was definitely excluded by the study of cerebrospinal fluid pressures. Lumbar punctures were made on 16 patients with changes in the eyegrounds. Slight or moderate elevation of pressure was found in only 5 of these patients, and this usually in association with an increase in the cell count and protein content. Lumbar punctures were made on 8 patients with normal eyegrounds, 2 of whom had increased cerebrospinal fluid pressures. These observations show that although in occasional in-

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stances the increased cerebrospinal fluid pressure may contribute to the edema of the disk it is not the underlying cause. Additional points of value in excluding papilledema are the vascular changes and the diffuse edema of the retina seen in the retinopathy of scrub typhus. Optic neuritis resembles the retinopathy of scrub typhus but was ruled out by the absence of visual disturbances and of a central scotoma. Also, optic neuritis is likely to be unilateral, whereas the retinopathy of scrub typhus is invariably bilateral. The retinopathy of hypertensive vascular and renal

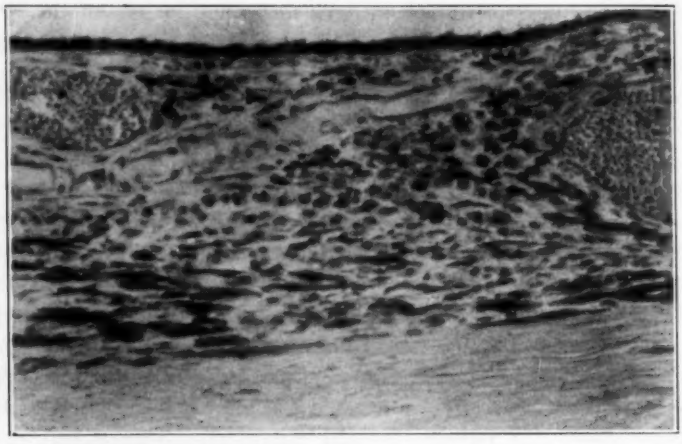

Fig. 8.—Photomicrograph, showing cellular infiltrate in the choroid. Army Institute of Pathology, Washington, D. C.

disease can be differentiated from that of scrub typhus by the characteristic changes in the retinal arteries. Hard, shiny exudates, particularly in the macular region, have not been seen in cases of scrub typhus.

OCULAR PATHOLOGIC CHANGES

The eyes of 9 patients were obtained at autopsy for pathologic study. The descriptions of the changes observed in these specimens and their interpretation, as recorded here, were prepared by Dr. Wilfred E. Fry.

These patients were too ill to permit examination with the slit lamp and the corneal microscope. The visual fields could not be taken. None had any visual complaints, nor was any impairment of visual function discovered while the patients were in sufficiently good condition to cooperate in the examination.

REPORT OF AUTOPSIES

Case 1.—W. F., a white soldier, aged 26, died of scrub typhus on the fifteenth day of his illness.

Ophthalmologic Consultation.—External Examination: External examination did not reveal anything significant.

Ophthalmoscopic Examination: Right eye: The media were clear. The outlines of the disk were slightly blurred. There was no evidence of edema. The optic nerve was normal. The retinal veins were engorged. No hemorrhages or exudates were present.

Left Eye: The picture was similar to that of the right eye.

Pathologic Report.—Cornea: The cornea was normal except for loss of the epithelium. There was no indication of edema, ulceration or necrosis.

Anterior Chamber: The angles were open. No exudates were present.

Iris and Ciliary Body: The iris showed no infiltration. The ciliary body was slightly infiltrated with mononuclear cells. No hyperemia of either the iris or the ciliary body was noted.

Lens: The lens was normal.

Choroid: The choroid was thicker than normal, with dilated vessels and considerable infiltration with mononuclear cells (fig. 8). No epithelioid or giant cells were present.

Retina: The vessels were dilated. No subretinal exudate or retinal hemorrhage was seen.

Optic Nerve: The disk did not appear edematous. No cellular infiltration was noted. The subarachnoid space was moderately dilated.

Sclera: The sclera was normal.

Impression.—The pathologic changes in this eye consisted in diffuse subacute choroiditis with possible slight involvement of the ciliary body.

Case 2.—J. C., a white soldier, aged 22, died of scrub typhus on the fifteenth day of his illness.

Ophthalmologic Consultation.—External Examination: Conjunctival hyperemia was rather intense.

Ophthalmoscopic examinations were made on the tenth and thirteenth days of his illness, and one-half hour before his death. On the tenth day the outlines of the disk were blurred in each eye. The veins were greatly engorged and appeared compressed at the arteriovenous crossings. On the thirteenth day of the illness definite edema of the disks and retina was noted. Retinal folds parallel with the disk were seen temporally in each eye. Examination one-half hour before his death revealed more pronounced edema of the disks and retina, the swelling of the disks measuring 1.5 D. A superficial retinal hemorrhage had appeared along the inferior temporal vessels, about 1 disk diameter from the disk.

Pathologic Reports.—Cornea: No abnormal changes were seen. There was partial loss of epithelium, but this was probably an artefact, due to injury in fixation and handling.

Anterior Chamber: The angles were open. In one angle was a small collection of mononuclear cells, some of which contained pigment granules.

Iris and Ciliary Body: Both structures were normal in appearance. No inflammatory changes or hyperemia was present. No posterior synechiae were seen.

Lens: The appearance did not suggest cataract.

Choroid: The choroid appeared one-third to one-half thicker than usual. Many of the vessels were dilated. Some were packed with red cells. At one point there were many red cells in the tissue. A mononuclear cell infiltrate, denser near the posterior pole, was present. Near the periphery there were foci of mononuclear cells.

Sclera: The sclera was normal.

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Retina: The retina was detached; this change was probably an artefact. The retina showed no abnormal changes except for dilated vessels.

Optic Nerve: The disk appeared moderately swollen and edematous (fig. 9), with retention of the physiologic cup and no infiltration. The subarachnoid space was dilated.

Impression.—The appearance of the disk was that of papilledema. There was an associated severe, subacute, diffuse choroiditis.

CASE 3.—L. P., a white soldier aged 24, died of scrub typhus on the fifteenth day of his illness.

Ophthalmologic Consultation.—External Examination: Ecchymosis had occurred into the right upper lid. Subconjunctival hemorrhages were seen above and temporal to the limbus in each eye.

Ophthalmoscopic Examination: The last ophthalmoscopic examination, made two days before death, revealed clear media. Edema of each disk, measuring 1 D.,

Fig. 9.—Photomicrograph, showing edema of the disk. Army Institute of Pathology, Washington, D. C.

was associated with edema of the retina. The disks were engorged and appeared veiled at the crossings. No hemorrhage or exudate was seen.

Pathologic Report.—Cornea: The epithelium was partly lost. There were no changes in Bowman's membrane, the stroma, Descemet's membrane or the endothelium. No keratic precipitates were observed. A subconjunctival hemorrhage lay near the limbus at one side.

Anterior Chamber: The angles were open. There was no exudate.

Iris and Ciliary Body: There was no infiltration or hyperemia. No posterior synechiae were seen.

Lens: The lens was normal.

Choroid: The choroid was thickened, and there was a diffuse mononuclear cell infiltration, with a sprinkling of large mononuclear cells. The vessels were engorged. No epithelioid or giant cells were seen.

Retina: The retina was detached. There were several dilated vessels. No subretinal exudate was seen.

Optic Nerve: The disk was edematous. Moderate dilatation of the subarachnoid space with some proliferation of the cells of the arachnoid was noted.

Impression.—Severe, subacute, diffuse choroiditis was present in each eye.

CASE 4.—T. B., a white soldier aged 34, died of scrub typhus on the sixteenth day of his illness.

Ophthalmologic Consultation.—External Examination: No abnormality was found except for an area of ecchymosis involving the right upper lid.

Ophthalmoscopic Examination: At the last examination, performed four days before his death, the media were clear; no edema of either disk or the retina could be seen in either eye; the veins were engorged, and no hemorrhage or exudate was present.

Pathologic Report.—Cornea: The epithelium was of uniform thickness and regular. Bowman's membrane was present and was uniform in appearance. The stroma fibers were regular and the nuclei normal in distribution and appearance. Descemet's membrane and the endothelium were intact. There were no keratic precipitates.

Anterior Chamber: The angles were open. There were no exudates.

Iris and Ciliary Body: There was no infiltration or edema, and no synechia was seen. Vascularity was not increased.

Lens: The lens was normal.

Retina: The retina was detached. Near the disk was a small subretinal exudate. There was no cellular infiltration or hemorrhage.

Choroid: A diffuse mononuclear cell infiltration involved nearly the entire choroid. The infiltration was slightly denser in the posterior third, and near the anterior portion several foci of infiltrates were noted. The vessels of the middle zone appeared dilated. No epithelioid or giant cells were seen.

Optic Nerve: About one-half the disk showed separation of the fibers suggesting edema. No other changes were noted.

Sclera: The sclera was normal.

Impression.—The pathologic diagnosis was moderately severe, subacute, diffuse choroiditis.

CASE 5.—W. L., a white soldier aged 28, died of scrub typhus on the twenty-second day of his illness.

Ophthalmologic Consultation.—External Examination: A subconjunctival hemorrhage was present above the limbus on the left eye.

Ophthalmoscopic Examination: Ophthalmoscopic examinations were carried out on six occasions, the last about one hour before death. At the time of the first examination, on the eleventh day of his illness, the only abnormality noted was moderate venous engorgement. The disks were slightly blurred at their poles. These changes progressed, until on the sixteenth day of his illness definite edema of the disk and macula was present bilaterally, and the venous changes were more prominent, the crossings being almost obscured and their outlines hazy in places. By the nineteenth day of his disease a dense preretinal hemorrhage, ½ disk diameter, had developed midway between and slightly below the disk and macula in the right eye. He also had a similar, but smaller hemorrhage in the macular area (fig. 10). The veins were tremendously engorged, appearing sausage like. One hour before

his death, examination revealed another hemorrhage in the right eye along the inferior temporal vessels, about 1½ disk diameters from the disk.

Pathologic Report.—Cornea: The cornea was normal.

Anterior Chamber: The angles were open, and there were no exudates.

Iris and Ciliary Body: There was no infiltration or hyperemia, and no posterior synechia was present.

Lens: The lens was normal.

Choroid: A mild, diffuse mononuclear cell infiltration was present. Over the posterior pole, on the temporal side of the disk, the vessels were conspicuously dilated.

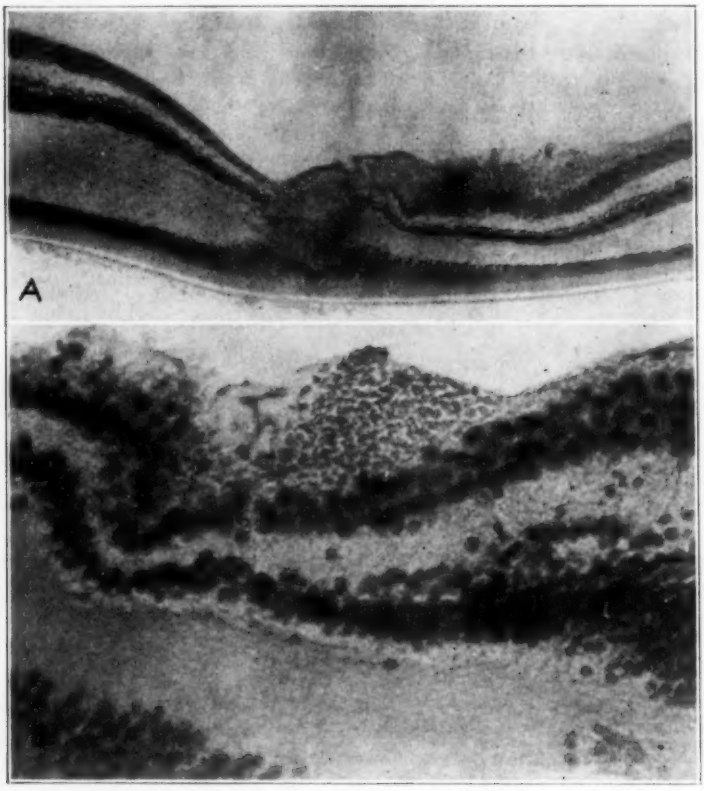

Fig. 10.—Preretinal hemorrhage in the macular region. *A*, low power; *B*, high power. Army Institute of Pathology, Washington, D. C.

Retina: The retina was detached, and there was no infiltration. A small hemorrhage was present in the retina near the macula.

Optic Nerve: One-half the disk was more prominent than normal, the fibers being separated as by slight edema and forced laterally under the adjacent retina. Physiologic excavation was present, the cup containing several mononuclear cells. The subarachnoid space was not dilated.

Impression.—The pathologic diagnosis was mild, subacute diffuse choroiditis with choroidal hyperemia. The changes in the disk suggested early papilledema.

CASE 6.—E. L., a white soldier aged 22, died of scrub typhus on the twentieth day of his illness.

Ophthalmologic Consultation.—External Examination: A massive subconjunctival hemorrhage had occurred temporally in each eye.

Ophthalmoscopic Examination: The only abnormality found on repeated examinations during the last two days before his death was moderate venous engorgement.

Pathologic Report.—Cornea: Most of the surface epithelium was lost, but the rest of the cornea appeared normal. There was no indication of ulceration. Keratic precipitates were not present.

Anterior Chamber: There was no exudate, and the angles were open.

Iris and Ciliary Body: There was no infiltration, edema or hyperemia, and no posterior synechia was noted. The pupils were dilated.

Lens: The lens was normal.

Choroid: There was dilatation of the vessels, chiefly of the middle layer, and involving approximately the posterior half of the globe. There were no cellular infiltrates.

Retina: The retinal detachment which was present was probably an artefact. No exudate or hemorrhage was seen. The vessels were slightly more prominent than usual.

Optic Nerve: The disk appeared normal. However, the vessels were dilated. The subarachnoid space was dilated.

Impression.—Hyperemia of the choroid and of the papilla was present.

CASE 7.—J. B., a white soldier aged 51, died of scrub typhus on the fifteenth day of his illness with an overwhelming infection.

Ophthalmologic Consultation.—External Examination: The conjunctivas were hyperemic. A massive subconjunctival hemorrhage was observed on the upper half of each eyeball.

Ophthalmoscopic Examination: Examination two days before death revealed only moderate venous engorgement.

Pathologic Report.—Cornea: No areas of infiltration or ulceration or keratic precipitates were seen.

Anterior Chamber: The angles were open. No exudate was present.

Iris and Ciliary Body: No infiltration or hyperemia was noted.

Lens: A patch of pigment was present on the anterior capsule of the lens, probably resulting from a posterior synechia that had been freed.

Choroid: The choroid was thicker than normal. The vessels were dilated. There was moderate mononuclear cell infiltration. The infiltration extended nearly to the ciliary body and, in the more anterior parts of the choroid, tended to occur in foci.

Retina: The retinal detachment which was present was an artefact. The vessels near the disk were moderately dilated.

Optic Nerve: There was no edema of the disk. There was moderate proliferation of the cells of the arachnoid; in addition, a number of mononuclear cells had infiltrated in from the subarachnoid space. The subarachnoid space was dilated.

Impression.—The diagnosis was moderate subacute, diffuse choroiditis and subacute perineuritis.

CASE 8.—E. K., a white soldier aged 23, died of scrub typhus on the thirteenth day of his illness.

Ophthalmologic Consultation.—External Examination: Mild conjunctival hyperemia was present in each eye.

Ophthalmoscopic Examination: The last examination, made five days before his death, revealed blurring of the outlines of the disks, with no definite evidence of edema. The veins were engorged.

Pathologic Report.—Cornea: There was partial loss of epithelium, probably an artefact. Bowman's membrane was intact at one point, where there was a small infiltrate. The stroma was normal except for a small area of connective tissue near the center of the anterior surface. Descemet's membrane and the endothelium were intact.

Anterior Chamber: The angles were open. There were no exudates.

Iris and Ciliary Body: There was no area of infiltration or hyperemia, and no posterior synechia was noted.

Lens: The lens was noncataractous.

Choroid: The choroid was thicker and more cellular than normal. There was a moderate diffuse mononuclear cell infiltrate of all the posterior half of the choroid.

Retina: The usual layers were present. There was no area of infiltration. Near the disk the veins appeared dilated, and at one point a hemorrhage in the fiber and internal nuclear layer was seen.

Optic Nerve: The fibers of the nerve at the disk were edematous. Physiologic cupping was preserved. There were no cellular infiltrates about the intact vessels.

Impression.—The changes in the disk were those of moderate papilledema. The choroid showed moderate subacute diffuse choroiditis.

Case 9.—J. M., a white soldier, aged 22, died of scrub typhus on the eleventh day of his illness.

Ophthalmologic Consultations.—External Examination: No abnormality was found.

Ophthalmoscopic Examination: The last examination, done within twenty-four hours of the patient's death, revealed only venous engorgement.

Pathologic Report.—Cornea: There was partial loss of the surface epithelium, probably an artefact. Bowman's membrane was intact. The stroma appeared normal. There were no changes in Descemet's membrane or in the endothelium and no keratic precipitates.

Anterior Chamber: The angles were open. There was no exudate.

Iris and Ciliary Body: There was no infiltration or hyperemia. The pupil was dilated. There was no posterior synechia.

Lens: The lens was normal.

Choroid: The choroid was thicker than normal. The vessels were dilated. There was a diffuse infiltration, consisting chiefly of small mononuclear cells. There were no epithelioid or giant cells. All the changes were more prominent in the posterior half.

Retina: The retinal detachment which was present was probably an artefact. There was no exudate or hemorrhage. Several of the vessels were dilated and filled with red cells. There was no subretinal exudate.

Optic Nerve: The fibers of the disk showed questionable edema. There were no other changes.

Impression.—The impression was that of mild subacute diffuse choroiditis.

The pathologic changes, therefore, consisted predominantly of posterior chroiditis, manifested by mononuclear cell infiltration. The edema of the disk and engorgement of the retinal vessels seen clinically were confirmed by the pathologic studies. This condition was comparable to

the infiltrative changes elsewhere in the body. Dr. Algernon B. Reese and Dr. Jonas Friedenwald also examined the slides and were in general agreement with the observations as recorded. Dr. Friedenwald,[9] however, stated the opinion that the choroidal changes might be compatible with the so-called septic choroiditis described by him in 1930 in patients dying of septicemia. After reviewing some of his original slides, he was less inclined to this opinion. The eyes of these patients who had died of scrub typhus showed a considerably more intense and diffuse infiltration of the choroid than did the ones of which he had written.

Dr. Henry Pinkerton, who has worked extensively with rickettsial diseases, studied sections from all these eyes for evidence of rickettsial inclusion bodies but found none. In a personal communication, he stated that from the general pathlogic point of view there was definite evidence of vasculitis and perivasculitis. He expressed the belief that there was proliferation of the capillary endothelium. These changes have been described as occurring in other tissues of the body in scrub typhus (Kouwenaar,[10], Lewthwaite, Corbett[11] and the *United States War Department Technical Bulletin*[12]).

These pathologic changes adequately explain the ophthalmoscopic changes of engorged retinal vessels, edema of the disk and retina and opacities in the vitreous. It is also not surprising that the anterior uveal tract is involved in some patients, resulting in ciliary flush and photophobia.

CLINICAL RELATION

The relation of the ocular abnormalities to other aspects of scrub typhus was studied in the second group of patients (159). The ophthalmic findings were correlated with data on the severity of the general symptoms and the occurrence of complications. These data were collected and organized by Sayen, Pond, Forrester and Wood as a part of their clinical report on scrub typhus in this hospital.

EXTRAOCULAR CHANGES

Subconjunctival hemorrhages late in the first week of the disease were frequently of diagnostic help, since they were uncommon and not so massive in the case of other diseases encountered in this area. Conjunctivitis was less specific but was occasionally helpful.

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9. Friedenwald, J. S., and Rones, B.: Some Ocular Lesions in Septicemia, Tr. Am. Ophth. Soc. **28**:286, 1930.

10. Kouwenaar, W.: Investigations on Rickettsial Diseases in Sumatra, Geneesk. tijdschr. v. Nederel.-Indië **80**:1119 (April 30) 1940.

11. Corbett, A. J.: Scrub Typhus, Bull. U. S. Army M. Dept., November 1943, no. 70, p. 34.

12. Scrub Typhus Fever, United States War Department, Technical Bulletin (T.B. Med. 31), Washington, D C., Government Printing Office, April 11, 1944.

INTRAOCULAR CHANGES

The most significant points in the relation of retinopathy to the general clinical picture of scrub typhus may be summarized as follows:

Type of Onset.—There was no correlation between the subsequent development of retinopathy and the presence of external ocular signs, ocular pain or photophobia, or the frequency of primary ulcers, rashes or lymphadenopathy.

Diagnosis.—The diagnosis of scrub typhus in a case of febrile disease rests on the presence of the ulcer at the site of the mite bite, the appearance of the rash and the presence of increased generalized lymphadenopathy. Later confirmation is provided by the titer of P. vulgaris O X K. The incidences of various diagnostic criteria were essentially as follows:

	Percentage
Primary ulcer	60
Rash	71
Lymphadenopathy	97
Agglutination of P. vulgaris O X K (in titer of 1:100 or more)	63

Thus, in a significant number of cases one or more of the criteria "essential" for early diagnosis were absent. In these clinically atypical cases the development of changes in the eyegrounds was of considerable diagnostic aid, because the retinopathy of scrub typhus was practically pathognomonic, at least in this geographic area. Similar changes are not known to occur in other acute febrile diseases. Cases of malaria, including the cerebral form, typhoid, meningitis and pneumonia have been personally observed, with no comparable retinal changes. Retinopathy develops on an average of three to four days before the agglutination reaction against P. vulgaris O X K becomes positive, thus affording diagnostic help before laboratory evidence is available. Thus, in several cases of undiagnosed fevers, the ophthalmologic findings first suggested scrub typhus. In a number of other cases in which scrub typhus was suspected, but not proved until later, the retinal findings helped to clinch the diagnosis.

Severity of Disease.—The distribution of the patients with and without retinopathy among the various groups into which this series was divided on the basis of clinical severity is shown in table 1. It can be

TABLE 1.—*Distribution of Cases of Scrub Typhus with and Without Retinopathy According to Clinical Severity*

	Group 1 Mild (48)	Group 2 Moderately Severe (48)	Group 3 Severe (33)	Group 4 Grave (18)	Group 5 Total (12)
Retinopathy	8	17	21	16	5
Normal fundi	40	31	12	2	7

seen that there is a definite increase in the frequency of retinopathy as the disease increases in severity (fig. 11). The lower incidence of retino-

pathy recorded in the fatal cases than in the cases of the severe and grave forms is probably attributable to the fact that death interrupted the development of the retinal lesion.

Complications.—Although wide dissemination of the rickettsial disease process is the rule, certain patients exhibited clearcut signs of dam-

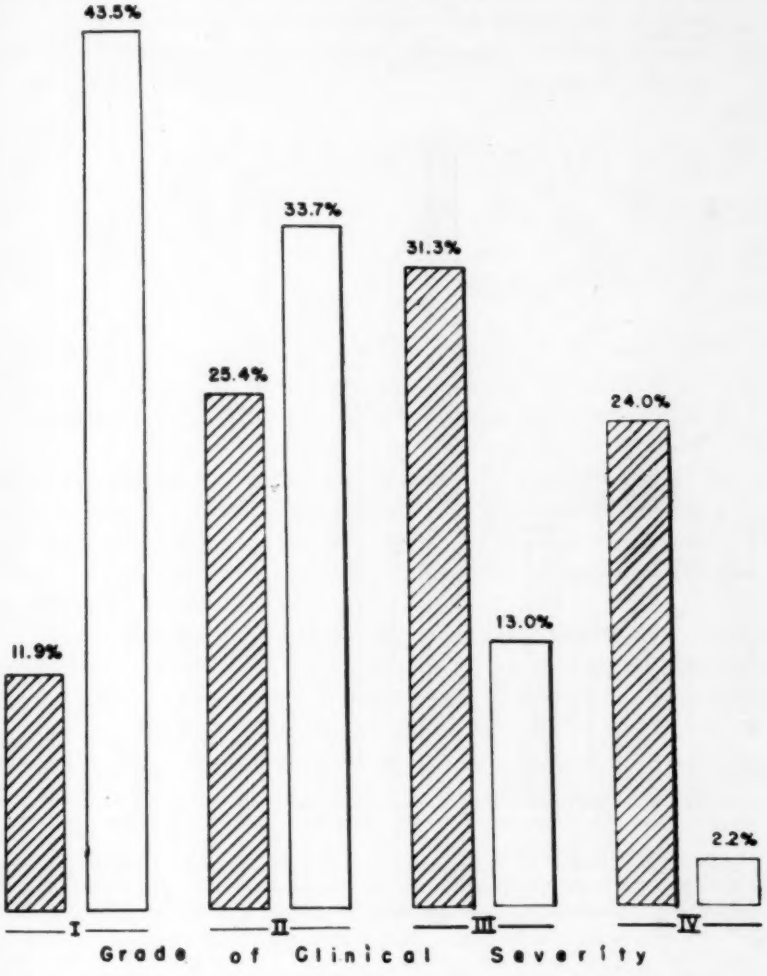

Fig. 11.—Relation of retinopathy to severity of the disease in patients with scrub typhus. The cross hatched areas represent patients with reninopathy; the clear areas, those without retinopathy. Army Institute of Pathology, Washington, D. C.

age to parenchymal organs, while others did not. Clinical and pathologic analysis of 159 cases and the hospital's experience in general demonstrated that extensive damage to important organs was largely confined to the

severely ill patients and that it played a major part in the outcome of the disease. When the following clinical signs appeared, a complication was said to be present, although the term is not thoroughly satisfactory:

Complication	Clinical Sign
Meningitis	Stiff neck
Encephalitis	Extreme restlessness, delirium, convulsions or coma
Myocarditis	Definite cardiac enlargement or pronounced electrocardiographic changes
Interstitial pneumonia	Cyanosis and greatly increased respiratory rate
Hepatitis	Jaundice
Interstitial nephritis	Albuminuria and granular casts, associated with decreased urinary volume, isosthenuria or uremia
Abnormal fluid balance	Edema and ascites

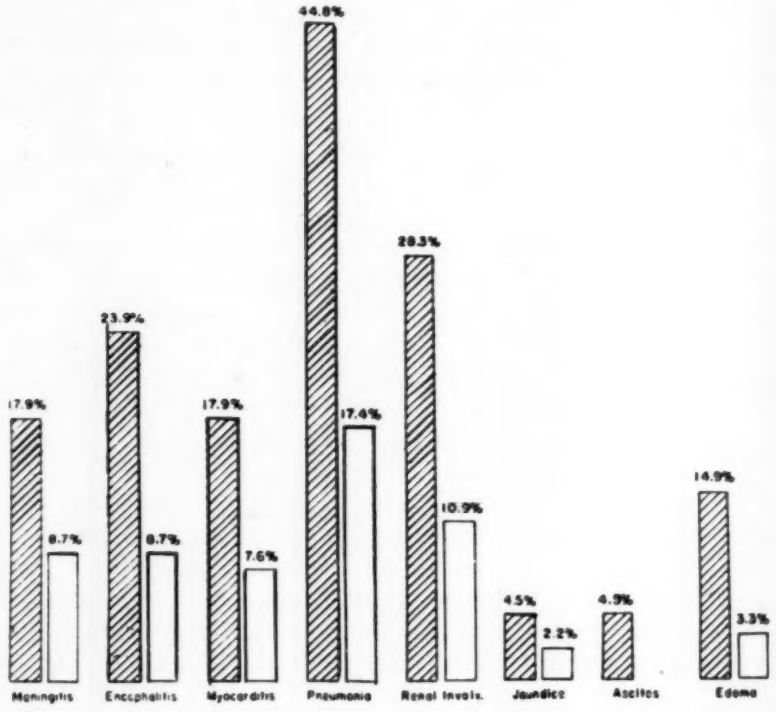

Fig. 12.—Relation of retinopathy to complications in patients with scrub typhus. Patients with retinopathy are represented by the cross hatched areas; those without retinopathy, by the plain areas. Army Institute of Pathology Washington, D. C.

There is a significant correlation between the incidence of these complications and that of retinopathy. A large number, 45 (67.2 per cent), of the 67 patients who had changes in the eyegrounds exhibited one or more complications. Conversely, such complications occurred in only 31 (33.7 per cent) of the patients with normal fundi. The incidence of complications in patients with and without retinopathy is illustrated in table 2 and is compared on a percentage basis in figure 12.

Convalescence.—One of the major problems in the management of convalescence from scrub typhus is to know how soon the patient has fully recovered. One can, as a rule, estimate the time fairly well on the basis of the general condition of the patient. In a patient with retinopathy, the time of disappearance of the retinal lesion furnished an additional objective criterion of recovery. It is reasonable to suspect that the disappearance of retinal changes parallels the disappearance of damage elsewhere. Consequently, no patient was returned to duty before his retinopathy had disappeared.

TABLE 2.—*Incidence of Complications in Patients with Scrub Typhus with and Without Retinopathy*

	Meningitis (20)	Encephalitis (24)	Myocarditis (19)	Pneumonia (46)	Jaundice (5)	Nephritis (29)	Edema (13)	Ascites (3)
Retinopathy	12	16	12	30	3	19	10	3
Normal fundi	8	8	7	16	2	10	3	0

SUMMARY

The eyes of 451 patients with scrub typhus were studied weekly for evidence of disease. The following external changes were seen: (1) conjunctival injection, 38 per cent; (2) subconjunctival hemorrhages, 6.4 per cent; (3) ecchymosis of the eyelids, 1.0 per cent; (4) eschar on the eyelid, 0.5 per cent; (5) fixation nystagmus, 0.5 per cent.

The following ocular changes were seen: (1) engorgement of veins, 67 per cent; (2) retinal edema, 36 per cent; (3) retinal hemorrhages, 6.6 per cent; (4) exudates, 4.9 per cent; (5) uveitis, 1.3 per cent; (6) vitreous opacities, 4.6 per cent.

Pathologic studies of eyes obtained at autopsy revealed that a subacute diffuse choroiditis was the basic lesion. Since changes in the fundus of this type had not been seen in other febrile diseases in this area, their presence was frequently helpful in diagnosis.

Since its disappearance presumably occurs at about the time of recovery from other parenchymal lesions of scrub typhus, it was used as a criterion for the stage of convalescence.

Lieut. Margaret Kabatt, Technician Third Class James A. Bergan and the entire staff of the eye, ear, nose and throat clinic aided in maintaining the records and in compiling the data in preparing this paper. Capt. Graham Eddy and the First Medical Museum and Arts Detachment furnished the illustrations.

313 South Seventeenth Street.

NEARLY ONE HUNDRED YEARS OF THE OPHTHALMOSCOPE

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NO INSTRUMENT in general medicine has influenced and developed a specialty as the ophthalmoscope has done for ophthalmology. In addition, the ophthalmoscope has been of importance in other branches of medicine, as it stimulated the development of instruments for examination of other parts of the body, such as laryngoscopy, rhinoscopy, gastroenteroscopy and cystoscopy. In this connection, it should be stated that the exact date of the discovery of these methods cannot be given. A report of the conditions which led to the discovery of the ophthalmoscope may be of interest to those less informed, and its publication is timely in view of the centenary of the day when von Helmholtz presented his discovery before the Physical Society in Berlin, on Dec. 16, 1850. There is no question in my mind that the sturdy ophthalmoscope will survive its one-hundredth birthday, a prospect which is not necessarily applicable to my own case, so that I have decided to write this report somewhat ahead of time.

Before entering on a discussion of the discovery of the ophthalmoscope, I wish to say a few words about von Helmholtz as a person. Von Helmholtz' life has been so admirably described in the monumental work of Königsberger[1] that I have taken much of the following account from this book. Von Helmholtz was born on Aug. 31, 1821, in Potsdam, the son and first child of a high school teacher, Ferdinand Helmholtz, who was then 30 years old. The boy was named Hermann Ludwig Ferdinand; he was a delicate child, passing the first seven years of his life principally indoors on account of illness, and mostly in bed, devoting himself to picture books, and especially to building blocks. During this period he received every encouragement on the part of his parents, who were much concerned about his mental development. In his seventh year his schooling began, but it was often interrupted by illness. He astonished his teachers by his grasp of geometry, which is ascribed to his playing with blocks. On the other hand, he was less successful in studies in which memory was a feature. Many years later he remembered how difficult

1. Königsberger, L.: Hermann von Helmholtz, Braunschweig, F. Vieweg & Sohn, 1902.

it was for him to learn by heart vocabularies, grammatical rules and connected prose. After finishing high school, he wanted to begin the study of natural science, but this his father's means did not permit, as the family now consisted of five children. It was finally arranged that the eager youth should take up mathematics and physics in connection with his early studies in medicine. After passing the examination, he obtained a preliminary scholarship in the Royal Medico-Surgical Friedrich-Wilhelm Institute. In consideration of certain conditions, he was allowed board and lodging during the years of his medical education at the University of Berlin, with the obligation that he serve in the army as physician for seven years after graduation. Von Helmholtz remained at this school from 1838 to 1842; as assistant in the library, he had access to mathematical textbooks, which, with intensive study in mathematics and physics, enabled him to do independent work and eventually to become, even at an early age, one of the celebrated mathematicians of his day.

He was most attracted to the physiologist Johannes Müller, of the medical faculty, as were his fellow students and intimates, Brücke, Dubois-Reymond and Ludwig, among whom a friendly and most active intellectual relationship existed. This was the period when great development was taking place in chemistry and mathematics, and mention need only be made of Lavoisier, Liebig, Coulomb, Ohm and, especially, Ernst Heinrich Weber. The last insisted on tracing back both the vital and the nonvital forces to physicochemical processes, independent of the mystic conception of life. Von Helmholtz held firmly to these views.

With a small microscope, which he purchased with his savings, he discovered the nerve fibers which arise from ganglion cells (discovered by Ehrenberg) and recognized their central origin, thus laying the histologic basis of all physiologic and pathologic processes in nerves.

This investigation, which particularly impressed Johannes Müller, was Helmholtz' doctor's dissertation, presented on Nov. 2, 1842. He then began his term as military physician, which lasted from 1843 to 1848. He performed his military duties with full conscientiousness and prepared himself for additional medical examinations, at the same time finding time for scientific work. He was occupied with the experimental investigation of a number of problems, especially those on fermentation and putrefaction, the nature of which he recognized as not being purely chemical, but vital as well, thus anticipating the ideas of Pasteur. Then the question of the origin of heat interested him greatly, and he recognized its important source in muscular action. He began the study of frog's muscles by means of a self-constructed electrical apparatus and determined the propagation of a nerve stimulus with methods which measured the smallest time intervals. All these investigations pointed to

a close interrelationship (von Helmholtz had grown to consider the idea of a vital force as a paradox and had arrived at the concept that neither energy nor matter can disappear). He therefore approached the problem of the preservation of energy at the same time that Robert Meyer and Joule came to the same conclusion by other lines of investigation. This subject was the title of an address which he delivered on July 23, 1847, before the Society of Physics; this paper was not accepted for publication in Poggendorf's annals because the article, in the editor's opinion, was speculative and without the experimental basis on which articles in this journal were supposed to depend. His friend, DuBois-Reymond, was disturbed by this rejection, and, on his suggestion, von Helmholtz published the article separately, with the preface by DuBois, in which he stated that it contained a program for modern natural science.

Though von Helmholtz had gained high esteem in scientific circles by his investigations, it was the discovery of the ophthalmoscope which made him famous throughout the world and connected his name for all time with this marvelous instrument.

This discovery took place, curiously, without any previous investigations or experiments bearing on this problem. As professor of physiology in Königsberg, and successor to Brücke, he demonstrated the lighting up of the pupil when light was projected into the eye with a mirror, an observation which had long been known. He expressed the belief that the rays of light which were returned from the eyeground must furnish a picture of this structure. If a convex lens was held between the observer and the observed in the course of the light rays, an inverted picture resulted, while if the observer came close to the observed the rays of light as they emerged from the eye produced a direct image of the eyeground. Thus, the discovery of the ophthalmoscope was based on many previous observations on the illumination of the pupil. I was not able to determine who was the first to observe the phenomenon of illumination of the pupil; without question, this was the most important observation which preceded the discovery of the ophthalmoscope and, in fact, contained the germ of the discovery.

The first presentation of von Helmholtz' discovery took place before the Physical Society of Berlin on Dec. 6, 1850. On December 7 von Helmholtz wrote the following letter to his father:

> On the occasion of my lectures on the physiology of the sense organs, I made a discovery which may be of real value to ophthalmology; it was so simple, requiring no more knowledge than what I had learned of optics in high school, that it is laughable that other people and I could have been so obtuse as not to have recognized it before.

A combination of lenses is necessary to illuminate the dark background of the eye through the pupil without using a dazzling light; then all the details can be seen more clearly than one sees the exterior of the

eye without magnification, because the transparent parts of the eye act in place of a loupe with a magnification of 20. The retinal blood vessels, arteries and veins, as well as the optic nerve, can be identified in their smallest branches. These were the words which revealed von Helmholtz' rapture as the first observer of the eyeground, a rapture which is shared by every one who observes for the first time the beautiful picture of the fundus with the miraculous aid of the ophthalmoscope. The letter continues:

> Formerly, a number of ocular diseases were designated under the term "black cataract," an unknown field, as the changes in the living and in the dead eye were not understood. My discovery permits the most specialized examination of the internal parts of the eye.

This statement shows that von Helmholtz, with the greatest modesty, regarded his findings as a scientific contribution—an observation rather than a discovery—but that from the first he was impressed with its practical importance. He added that he proclaimed before the Physical Society of Berlin that the instrument was like "Columbus' egg, which is to be most carefully treated." He went on to say that a more practical and improved model than the *papier maché* contrivance was being manufactured and that examinations by the head ophthalmologist in Berlin were then to be made and reported later.

His great contemporary, von Graefe, was equally impressed with the practical importance of the ophthalmoscope, and in the later years opened up new fields in ophthalmology with this instrument. Von Graefe wrote to von Helmholtz on Nov. 7, 1861, as follows:

> My dear Professor: Forgive me as one not known to you for addressing this letter to you, to ask you about a subject of the greatest interest to me. Last summer, Professor Brücke, in Vienna, told me that you had succeeded in constructing an instrument which permitted the examination of the living retina. As I have devoted myself to ophthalmology with particular enthusiasm for a number of years, I am anxious to try out this much longed-for diagnostic instrument, to the advantage of science in general. I have promised to forward models to my London and Paris colleagues, Dr. Bowman and Dr. Desmarres. The former, who is most interested in the scientific development of our specialty and has a large service at Moorfields Hospital, is particularly eager to receive an early model. I have asked Dörfel, my local instrument maker, to make the instrument, and I want first to compare it with one which was made in Königsberg under your supervision. I am therefore begging you to ask your mechanic to send to Berlin one or two of the instruments constructed according to your specifications. With the hope that you will pardon my presumption because of my interest in the subject, believe me, yours most truly, Dr. A. von Graefe, physician-operator in Berlin.

In the years following the discovery of the ophthalmoscope, von Helmholtz published his "Optique Physiologique,"[2] and thereby created the theoretic foundation of ophthalmology; this was followed by a series

2. von Helmholtz, H.: Optique physiologique, Paris, V. Masson & fils, 1867.

of acoustic, as well as mathematical and physical, investigations and transformed in 1871 the medical von Helmholtz to the highest ranking professor of physics in the University of Berlin, thirty-two years after he had begun his studies in Berlin at the military academy. At this time he was invited to become professor of experimental physics at Cambridge (England), under the most flattering conditions.

One of the more important contributions which he made at this time was to organize and plan the Royal Physico-Technical Institute at Charlottenberg, of which he acted as president up to the date of his death.

With his recognition in all parts of the world, it was natural that he should be elected as a worthy representative of his country and of his university at meetings in foreign countries, such as the Electrical Congress, in Paris, in 1882; the Geodetic Congress, in Rome, in 1883; the celebration of the six hundredth anniversary of the celebrated medical school in Montpellier, in 1890, and the World's Fair in Chicago, in 1893. On every occasion he was received with the greatest enthusiasm.

In Montpellier, he said, speaking of the unifying force of science:

> No one of us can work scientifically without aiding his own country, and at the same time the entire civilized world. All nations that work in science have a common field and necessarily help one another. This truth must finally prevail and lead to a friendly relationship in the world.

He concluded that it is medicine which has always practiced this peace-producing habit of science and has presented it before the eyes of the world, even in the moment of the emotional reactions of war.

Julienstrasse 50 (XVIII).

CHOLINESTERASE IN THE AQUEOUS OF THE EYE

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EVER SINCE the discovery of cholinesterase by Loewi and Navratil[1] in 1926, the number of experimental investigations concerning this vital enzyme has been almost legion. Cholinesterase is capable of converting acetylcholine into the relatively inactive choline and acetic acid. Consequently, it represents a new tool in the study of autonomic activities.

In the past twenty-two years the cholinesterase content of well nigh every tissue in the human and lower organisms has been noted. The tissues of the eye have not been neglected. Interestingly enough, it is concerning them that one of the few controversies exists.

Cholinesterase is not a difficult substance to work with. It is relatively stable. Vahlquist[2] stated that blood plasma at room temperature in a sealed tube retains its cholinesterase activity for at least a week. Stedman[3] stated that serum, if sterile, retains its cholinesterase activity for months. Recently, many new methods have been devised for accurate determination of the enzyme.

Considerable importance within recent years has been ascribed to the autonomic nervous system in the genesis of ophthalmic diseases. The possibility that the cause of glaucoma lies in a disturbance in central autonomic pathways has been suggested by Schoenberg. This work is supported by pupillographic records from glaucomatous patients.[4]

Funds donated by the Jewish Hospital of Brooklyn aided in the performance of this work.

1. Loewi, O., and Navratil, E.: Ueber humorale Uebertragbarkeit der Herznervenwirkung: X. Ueber das Schicksal des Vagusstoffs, Arch. f. d. ges. Physiol. **214**:678, 1926.

2. Vahlquist, B.: On Esterase Activity of Human Blood Plasma, Skandinav. Arch. f. Physiol. **72**:133, 1935.

3. Stedman, E., and Stedman, E.: Relative Cholinesterase Activities of Serum and Corpuscles from Blood of Certain Species, Biochem. J. **29**:2107, 1935.

4. Löwenstein, O., and Schoenberg, M.: Nervous Factor in the Origin of Simple Glaucoma, Arch. Ophth. **31**:384 (May) 1944; Pupillary Reactions of the Seemingly Unaffected Eye in Clinically Unilateral Simple Glaucoma: Pupillographic Contributions to the Diagnosis of Glaucoma in the Preclinical Stage, ibid. **31**:392 (May) 1944.

More recently, Bloomfield[5] studied the aqueous of normal eyes and observed that the fluid caused an isolated frog heart to decrease its amplitude of contraction. On the contrary, aqueous from the eyes of glaucomatous patients caused a slight increase in the amplitude. He attributed the latter to a parasympathetic deficiency in the aqueous and suggested this as a possible etiologic factor in the causation of glaucoma. Rados[6] studied the blood cholinesterase levels of patients with glaucoma but could find no significant deviations from normal values. Pletneva, Raeva and Veronina[7] examined the aqueous of a large number of patients with glaucoma and of others with cataract. In 52 per cent of the patients the aqueous was sympathicotropic and in 34 per cent vagotropic. Hence, it would seem that the cholinesterase activity of normal and pathologic eyes would be of considerable value in establishing the autonomic genesis of many disorders.

Cholinesterase has been demonstrated in all the tissues of the eye. Herrmann and Friedenwald[8] studied the cholinesterase content of the ciliary processes and the choroid plexus. They showed that these tissues contain considerable cholinesterase, although there is no evidence that the secretory activity of either is cholinergic. Brücker[9] studied the occurrence and distribution of cholinesterase in the uvea. Anfinsen[10] showed its occurrence in the retina, and Weve and Fischer[11] demonstrated cholinesterase in the subretinal fluid in cases of detached retina. The vitreous has been shown by many to contain cholinesterase. This work has been done by many, and no controversy has existed. However, there has been a dispute over the cholinesterase content of the aqueous.

In 1930, Plattner and Hintner,[12] working on cats, demonstrated the presence of cholinesterase in the aqueous. Velhagen,[13] in work done from

5. Bloomfield, S.: Relative Deficiency of Parasympathetic Activity in Aqueous of Eyes with Chronic Simple Glaucoma, Arch. Ophth. **37**:608 (May) 1947.

6. Rados, A.: Blood Cholinesterase Values of Patients with Glaucoma, Arch. Ophth. **30**:371 (Sept.) 1943.

7. Pletneva, N.; Raeva, N., and Veronina, E.: Biologic Analysis of Aqueous Humor in Glaucomatous Patients, Vestnik oftal. **13**:462, 1938.

8. Herrmann, H., and Friedenwald, J. S.: Cholinesterase Content of Choroid Plexus and Ciliary Processes, Bull. Johns Hopkins Hosp. **70**:14, 1942.

9. Brückner, R.: Auge und Cholinesterase: Vorkommen und Verteilung von Cholinesterase in der Uvea, Ophthalmologica **106**:200, 1943.

10. Anfinsen, C. B.: Distribution of Cholinesterase in Bovine Retina, J. Biol. Chem. **152**:267, 1944.

11. Weve, H. J. M., and Fischer, F. P.: Cholinesterase Content of Subretinal Fluid in Detached Retina, Ophthalmologica **96**:348, 1939.

12. Plattner, F., and Hintner, H.: Die Spaltung von Acetylcholin durch Organe und trakte Körperflüssigkeiten, Arch. f. d. ges. Physiol. **225**:19, 1930.

13. Velhagen, K.: Ueber die antagonistischen Beziehungen zwischen Hinterlappenhormonen und Insulin, Arch. f. exper. Path. u. Pharmakol. **142**:127, 1929;

1929 to 1936, showed also that cholinesterase was present in the normal aqueous. However, the first objection to these findings arose when Uvnäs and Wolff,[14] working on bovine eyes, were unable to demonstrate cholinesterase in the aqueous. To explain this contradiction, they offered the possibility that previous investigators had effected too great an emptying of the anterior chamber of the eye, thus causing seepage of cholinesterase-rich vitreous into the specimen. Brückner,[15] in 1943, working on horses and cows, stated that cholinesterase is a regular component of the aqueous and suggested that the enzyme arises from sources other than the blood. Further, he stated that the aqueous of the horse was richer in cholinesterase than the vitreous.

Before discussing the results of the present work, it might be advantageous to attempt to settle the dispute purely on theoretic grounds, i.e., by what is known of the chemistry of enzymes and of the aqueous.

Northrop[16] showed that enzymes obtained in crystalline form had identical physical properties as crystalline proteins. Previous to this it had been known that enzymes were in some way associated with proteins. However, it was not definitely established whether enzymes were proteins or were linked in some way with proteins. However, Northrop showed that the crystalline enzyme, when devoid of all other protein substances, still had the identical properties of a protein. Bodansky[17] concluded that every enzyme which has thus far been obtained in crystalline form has been a protein.

Further work has shown that the property of an enzyme may be due to a union between a protein group and another large chemical group. That is, many enzymes are conjugated proteins (a protein whose molecule is combined with another, nonprotein, group). A common example of a conjugated protein is hemogoblin (heme plus globin). At any rate, it has been established that every known enzyme is a protein. Cholinesterase has been shown by Engelhart and Loewi[18] to be enzymatic in nature. Consequently, cholinesterase is in all likelihood a protein.

Einleitende Untersuchungen über das Vorkommen aktiver und neurotroper Substanzen im Auge, Arch. f. Augenh. **103**:424, 1930; Ueber das Vorkommen depressorischer Substanzen im Auge, ibid. **104**:546, 1931; Zur Frage der vagotropen Substanzen im Auge, ibid. **105**:573, 1932; Die hypoxämische Farbenasthenopie, eine latente Störung des Farbensinnes, ibid. **109**:605, 1936.

14. Uvnäs, B., and Wolff, H.: On Occurrence of Acetylcholine Esterase in Aqueous Humour and Vitreous Body, Acta ophth. **16**:157, 1938.

15. Brückner, R.: Auge und Cholinesterase, Ophthalmologica **105**:37, 1943.

16. Kunitz, M., and Northrop, J. H.: Crystalline Chymo-Trypsin and Chymo-Trypsinogen Isolation: Crystallization and General Properties of New Proteolytic Enzyme and Its Precursor, J. Gen. Physiol. **18**:433, 1935.

17. Bodansky, M.: Introduction to Physiological Chemistry, ed. 4, New York, John Wiley & Sons, Inc., 1938, p. 133.

18. Engelhart, E., and Loewi, O.: Fermentative Azetylcholinspaltung im Blut und ihre Hemmung durch Physostigmin, Arch. f. exper. Path. u. Pharmakol. **150**:1, 1930.

It is known that the protein content of the normal aqueous is almost nil. According to Duke-Elder,[19] the ratio of the protein in the aqueous to that in serum may be expressed for different animals as follows: horse, 1:370; cow, 1:440; rabbit, 1:140. The proteins in the aqueous are the same as those in the serum of the same animal. In addition, they maintain the same relative proportions in the aqueous and in the blood. The same may be said for immune bodies and for enzymes.

Thus far, two important points have been stated: 1. The protein content of normal aqueous is almost nil. 2. Cholinesterase is an enzyme, and

TABLE 1.—*Cholinesterase Determinations on Normal Aqueous of the Cat**

Specimen No.	Amount of Aqueous, Cc.	Amount of 0.02 Normal Sodium Hydroxide, Cc.
1	0.7	0.06
2	0.4	0.00
3	0.4	0.05
4	0.75	0.013
5	0.75	0.013
6	0.6	0.00
7	0.7	0.00
8	0.2	0.00
9	0.85	0.00
10	0.8	0.00

*Results are expressed as the number of cubic centimeters of 0.02 normal sodium hydroxide required to neutralize the acid produced from a 1.2 molar solution of acetylcholine by the test solution. With the method used, the values can be reproduced to ±0.05 cc. Therefore, the results indicated in the table show that the normal aqueous of the cat is essentially negative for cholinesterase.

consequently a protein. Therefore, on theoretic grounds, one would not expect to find significant quantities of cholinesterase in the aqueous.

PRESENT INVESTIGATION

EXPERIMENT.—*Procedure.*—Ten normal cats were chosen. Less than 1 cc. of aqueous was removed from the right eye of each animal. The paracentesis was performed by direct puncture with a 26 gage needle on a tuberculin syringe. In no case was all the aqueous removed. Cholinesterase determinations were made on all the specimens according to the method to be described. The results are shown in table 1.

Method of Determination.—A modified Stedman technic[3] was used. All determinations were made at 37.5 C., at a *p*H of 7.4 for a period of twenty minutes. The substrate used was a 1.2 molar solution of acetylcholine. The test solution (cholinesterase) was added until the acid liberated by the reaction was neutralized.

19. Duke-Elder, W. S.: Textbook of Ophthalmology, London, Henry Kimpton, 1932, vol. 1, p. 427.

The values are expressed as cubic centimeters of 0.02 normal sodium hydroxide. The average normal value for plasma is 3.33 cc.; that for whole blood, 5.8 cc.

EXPERIMENT 2.—Four normal cats were chosen. From each animal 1 cc. of the aqueous of the right eye was removed and discarded. The second aqueous, which formed within five minutes, was removed and saved (A specimen). The third aqueous from the 4 eyes was then withdrawn and saved (B specimen). Cholinesterase deterinations were made on the saved A and B specimens.

The results are shown in table 2.

All A specimens represent the first re-formed aqueous, and all B specimens, the second re-formed aqueous. The average value for the first re-formed aqueous (A) was 0.68 cc.; that for the second re-formed aqueous (B) was 0.92 cc. The average A specimen showed a cholinesterase activity which was about 21 per cent, and the average B specimen an activity which was 28 per cent, of normal plasma cholinesterase.

TABLE 2.—*Cholinesterase Values of Second Aqueous of 4 Cats**

Specimen No.	Amount of Aqueous, Cc.	Amount of 0.02 Normal Sodium Hydroxide, Cc.
17 A	0.40	0.70
18 A	0.75	0.64
19 A	0.85	0.68
20 A	0.70	0.70
17 B	0.60	0.98
18 B	0.45	0.80
19 B	0.35	0.97
20 B	0.67	0.94

*The amount of cholinesterase is expressed in cubic centimeters of 0.02 normal sodium hydroxide required to neutralize the acid produced from a 1.2 molar solution of acetylcholine by the test solution.

COMMENT

Since cholinesterase is a protein, and since proteins enter the normal aqueous in only minute quantities, one should not expect to find significant amounts of cholinesterase in the normal aqueous.

It is well known that the aqueous which enters the eye after a paracentesis is relatively rich in protein. The protein content of this new aqueous is about 30 per cent of the value for plasma. Since the new aqueous shows a relatively large amount of cholinesterase activity (21 per cent of plasma), it is reasonable to assume that the cholinesterase entered with the protein fraction. Consequently, this is another property which cholinesterase has in common with the proteins of the blood. A second paracentesis of an eye causes a still greater inflow of protein, and therefore the enzyme content increases still further.

In glaucoma, the protein content of the aqueous has never been known to be increased. Consequently, cholinesterase cannot be present in

the aqueous of a glaucomatous eye. This supposition is indirectly supported by the work of Pletneva, Raeva and Veronina,[7] who examined the aqueous of a large number of patients with glaucoma for sympathetic and parasympathetic activity. They found parasympathetic activity in about one-half the subjects and sympathetic activity in the other half. If autonomic disturbances are definitely established in this disease, another problem arises, i.e., how to account for the normal cholinesterase levels.

SUMMARY

The controversy over the presence of cholinesterase in the normal aqueous is discussed.

On purely theoretic grounds, there should be at best only faint traces of cholinesterase in the aqueous, since the enzyme is a protein.

Aqueous from the eyes of 10 normal cats showed either no, or insignificant traces of, cholinesterase.

The first and second aqueous after paracentesis showed marked cholinesterase activity.

The amount of cholinesterase in the aqueous after a paracentesis as compared with cholinesterase values for plasma parallels closely the amount of protein in the aqueous after a paracentesis as compared with plasma protein levels.

ELECTROPHORETIC PATTERNS OF CONCENTRATED AQUEOUS HUMOR OF RABBIT, CATTLE AND HORSE

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ANALYTIC DATA concerning the naturally occurring proteins of the aqueous humor are scant, the measurements presenting two major difficulties: the small amount of available fluid and its low protein content. Duke-Elder[1] separated albumin and globulin in pooled aqueous of three species of animals by fractional precipitation with neutral salts and found the albumin-globulin ratio similar to that occurring in the serum of the respective species. The specific identity of the fractions separated from the horse aqueous with serum albumin and serum globulin of this species was demonstrated by Duke-Elder[1] on the basis of their antigenic properties. Kronfeld[2] obtained in several instances positive precipitin reactions with human aqueous on serums of rabbits which were immunized with human serum albumin and globulin. It was assumed, therefore, that the proteins in the aqueous of normal eyes in the examined species originated mainly in the blood serum, with a possible inconspicuous admixture of proteins arising from other sources (cytolysis, lens proteins).

Attempts to characterize the aqueous proteins by the moving boundary electrophoretic method perfected by Tiselius have not been reported. This method permits the observation in a homogeneous electric field of the mobilities of various components of a protein mixture and of the concentration of each component as measured by the refractive index increment of its boundary. The mobilities depend on the average surface charge per unit area of the molecules, and the direction of migration depends on the sign of this charge. From the electrophoretic pat-

This study was supported by the Knapp Memorial Foundation.

From the Department of Ophthalmology and the Electrophoresis Laboratory, Columbia University College of Physicians and Surgeons.

1. Duke-Elder, W. S.: The Nature of the Intraocular Fluids, Brit. J. Ophth., 1927, supp. 3.

2. Kronfeld, P. C.: The Protein Content of the Aqueous Humor in Man, Am. J. Ophth. **24**:1121, 1941.

tern, the relative concentration of the individual fractions can be approximately computed by integrating the area under each peak of the pattern. Kabat, Landow and Moore[3] determined the electrophoretic pattern of cerebrospinal fluid of individual patients by concentrating large volumes of the fluid (up to 80 cc.) to about 2 cc. for measurement in a microcell of this capacity. A similar technic was used in the present study.

TECHNIC

A total of 40 cc. of aqueous was withdrawn from the eyes of 80 normal rabbits, with the use of local anesthesia induced with dibucaine hydrochloride, 0.1 per cent, with the usual precautions. A total of 5.8 cc. of aqueous was aspirated from 20 rabbits one hour after treating the eyes iontophoretically from the anode with a solution of 0.1 per cent physostigmine salicylate U.S.P. and 0.1 per cent histamine phosphate U.S.P. at 1 milliampere for one and one-half minutes. In 12 eyes severe inflammation was produced by intravitreal injection of 0.1 cc. of staphylococcus toxin, according to the technic described in a previous paper.[4] A total of 2.9 cc. of aqueous was withdrawn when the inflammation appeared at its height. In this series, 6 mg. of sodium citrate per cubic centimeter of fluid was added to prevent coagulation.

Forty-five cubic centimeters of aqueous was collected from the eyes of freshly slaughtered cattle one to three hours after death. Seventy cubic centimeters of aqueous of horses was obtained during the process of bleeding the animals to death.

In all instances the protein content of the original aqueous fluid and that of the concentrated samples were determined nephalometrically according to the method of Looney and Walsh,[5] using the microcuvette designed for the Coleman nephelometer. With the technic used by Kabat, Moore and Landow for cerebrospinal fluid, the aqueous was placed for concentration in a cellophane dialyzing membrane and exposed to nitrogen having a constant pressure of 250 mm. of mercury at refrigerator temperature for several days. The aqueous, concentrated to a volume of about 2 cc., was then redialyzed for twenty-four hours against a buffer 0.02 molar with respect to sodium phosphate and 0.15 molar with respect to sodium chloride (p_H 7.4). The electrophoretic determination of the protein components in the samples of concentrated aqueous was carried out in a microcell having a capacity of 2 cc. The apparatus and method have already been adequately described.[6] The aqueous humors of rabbit, horse and cattle were concentrated 20, 35, and 22.5 times, respectively. Rabbit aqueous from eyes treated with

3. Kabat, E. A.; Landow, H., and Moore, D. H.: Electrophoretic Patterns of Concentrated Cerebrospinal Fluid, Proc. Soc. Exper. Biol. & Med. **49**:260, 1942. Kabat, E. A.; Moore, D. H., and Landow, H.: An Electrophoretic Study of the Protein Components, J. Clin. Investigation **21**:571, 1942.

4. von Sallman, L., and Di Grandi, J.: Controversial Points in Ocular Penicillin Therapy, Arch. Ophth., to be published.

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6. Tiselius, A.: A New Apparatus for Electrophoretic Analysis of Colloidal Mixtures, Tr. Faraday Soc. **33**:524, 1937. Longsworth, L. G.: Recent Advances in the Study by Electrophoresis, Chem. Rev. **39**:323, 1942. Ross, V.; Moore, D. H., and Miller, E. G., Jr.: Proteins in Human Seminal Plasma, J. Biol. Chem. **144**:667, 1942.

histamine and physostigmine was concentrated 2.9 times. The aqueous of the eyes given injections of staphylococcus toxin was used unconcentrated. All the serums were diluted with 3 volumes of phosphate saline buffer at p_H 7.4 before analysis. The concentration of the electrophoretically characterized components in the original aqueous was calculated by multiplying the total protein content of the fluid by the percentage composition of that component as measured in the electrophoretic pattern. The method is subject to a small error, since the specific refractive indexes of all the components may not be identical. With this technic, the mobilities and concentrations of the protein components of normal and pathologic rabbit aqueous and of normal cattle and horse aqueous were determined.

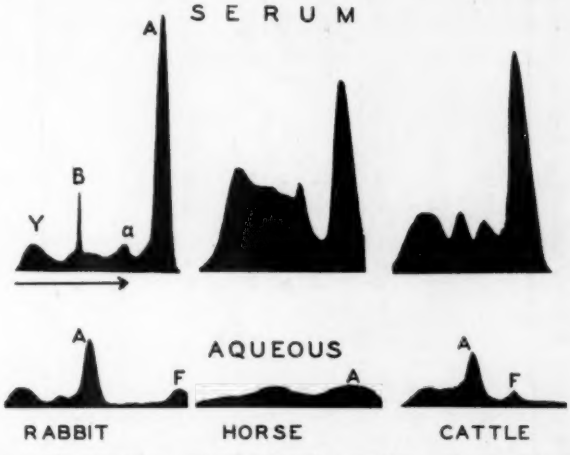

Chart 1.—Comparative electrophoretic pattern of serums and aqueous humors. Before analysis, all the serums were diluted with 3 volumes of phosphate saline buffer at a p_H of 7.4. The aqueous humor of rabbit, horse and cattle were concentrated 20, 35 and 33.5 times, respectively, by dialysis under pressure.

RESULTS

The results are presented in the accompanying table. They show, as is illustrated by the patterns (chart 1), that the albumin-globulin ratios for the normal aqueous of the three species of animals were similar to those of the respective serums. The rabbit and horse aqueous contained only two globulins, however, and the globulins of the cattle aqueous were poorly defined. The albumin-globulin ratio for the aqueous of rabbits was 1.4; that for cattle aqueous, 1.1, and that for horse aqueous, 0.74. The ratio was raised to 2.34 for the aqueous of rabbit eyes treated with vasodilators. The normal aqueous of rabbits and that of cattle contained a small amount of a component with a mobility greater than that of albumin; but, because of its small magnitude, identification was not attempted (E in chart 1). The aqueous of rabbit eyes which had been subjected to iontophoretic treatment with vasodilators also did not reveal peaks in the electrophoretic pattern for β-globulin or fibrinogen (chart 2*A*), whereas these fractions were present in the pattern of the aqueous

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Electrophoretic Fractionation of Serums and Aqueous Humors of Rabbit, Horse and Cattle

Species	Material	Treatment	Percentage Composition Globulin						Albumin-Globulin Ratio	Globulin Mobilities					
			Fast Component	Albumin	α Globulin	β Globulin	Fibrinogen	γ Globulin		Fast Component	Albumin	α Globulin	β Globulin	Fibrinogen	γ Globulin
Rabbit	Serum; aqueous	Normal		56.1	12.7	17.2		14.0	1.27		5.25	3.36	2.79		1.08
			16.4	49.1	7.3			27.2	1.42*	12.2	5.96	3.82			1.18
Horse	Serum; aqueous	Normal		36.7	12.3	21.6		29.4	0.58		5.30	3.44	2.50		0.96
				42.5		42.5		15.0	0.74		5.06		2.50		0.72
Cattle	Serum; aqueous	Normal		53.2	9.5	11.7		25.6	1.14		5.20	3.63	2.63		1.25
			9.3	48.2	13.0			29.5	1.13*	9.6	5.50	3.28			1.18
Rabbit	Aqueous	After iontophoresis with histamine and physostigmine		61.5	14.1			24.4	2.34†		5.2	3.3			1.00
Rabbit	Aqueous	After injection of staphylococcus toxin		63.8	3.8	12.4	8.5	11.5	1.13		4.50	3.40	2.63	1.90	1.25

*Fast component omitted.
†Fibrinogen omitted.

proteins of rabbits with endophthalmitis induced with staphylococcus toxin (chart 2*B*).

COMMENT

The data on serums of rabbits, cattle and horses refer to individual samples of each species but fall into the range of values reported by Moore[7] and by Svensson[8] in extensive investigations of species differences in serum protein patterns. Small quantities of both albumin and globulin were found to occur in the aqueous in about the same ratio as they do in the serum. Two differences, however, appeared: 1 α and β globulins were either low or absent in the aqueous. 2. The aqueous of normal rabbit and cattle eyes contained a component having a mobility greater than albumin.

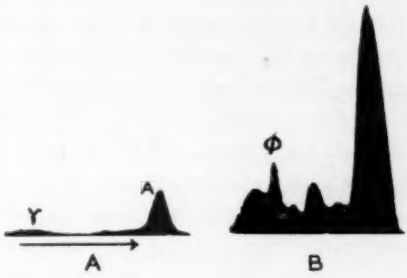

Chart 2.—Rabbit aqueous after eyes had (*A*) been subjected to iontophoretic treatment with solution of physostigmine and histamine or (*B*) staphylococcus toxin had been injected. The aqueous humor of eyes treated with iontophoresis (*A*) was concentrated 2.9 times; that of eyes given injections of toxin (*B*) was not concentrated.

The absence of β globulin may be significant, since the component is partially ether soluble and carries the opalescence of serum.[9] The fast component is possibly hyaluronic acid or a hyaluronic acid-protein complex. The presence of this component in serum, however, was not excluded, since the former was concentrated about twenty times in order to make its appearance in the aqueous, whereas the serums were diluted four times. A similar fast component was also observed in concentrated spinal fluid. There was no reason to assume that the boundary which indicated the small fast component belonged to the false moving boundaries described by Svensson,[10] because the protein content of the samples

7. Moore, D. H.: Species Differences in the Serum Protein Patterns, J. Biol. Chem. **161**:21, 1945.

8. Svensson, H.: Electrophoresis by the Moving Boundary Method: A Theoretic and Experimental Study, Ark. Kemi. min. geol. **10**:1, 1946.

9. Blix, G.: Electrophoresis of Lipid-Free Blood Serum, J. Biol. Chem. **137**: 495, 1941.

10. Svensson, H., cited by Blix,[9] p. 161.

was low and the ionic strength of the buffer high. In addition, no false boundaries have been observed in this phosphate buffer mixture.

The resemblance to plasma of the pooled rabbit aqueous in the experiments with staphylococcus toxin suggested that in the acute stage of inflammation all the plasma proteins were drawn into the aqueous. The iontophoretic introduction of the physostigmine and histamine salts gave rise to an increased content of protein in the aqueous (about 300 mg. per cubic centimenter) with an almost twofold increase in the albumin-globulin ratio. It seemed that the transient capillary dilatation rendered the wall of the vessel permeable to the relatively small albumin molecule, whereas the components of greater molecular size were retained by the membranes of the blood-aqueous barrier. Such elevation of the albumin-globulin ratio was observed to an even higher degree by Ayo and Meyer[11] in rabbit aqueous after the intravenous injection of Escherichia coli toxin. It is known that a light beam passing through a solution of albumin produces less Tyndall scattering per unit of nitrogen than it does in solutions of the other serum proteins. This optical behavior and the demonstrated shift of the albumin-globulin ratio in the aqueous of moderately irritated eyes may explain some of the discrepancies between the colloidometrically measure intensity of the aqueous flare and the respective protein content of the aqueous of human eyes.[12]

SUMMARY

Electrophoretic patterns of pooled aqueous humors from rabbit, horse and cattle were compared with those of the serums of the respective species. Besides the great difference in the total protein concentration of these body fluids, the aqueous exhibited a fast component not apparent in the serum and contained only two globulin components.

In the aqueous of inflamed eyes of rabbits the presence of albumin, α, β and γ globulins, and fibrinogen was indicated.

Vasodilation in the anterior segment of the eye induced with histamine and physostigmine resulted in a considerable increase in the albumin: globulin ratio.

630 West One Hundred and Sixty-Eighth Street.

11. Ayo, C., and Meyer, K.: Protein Content of Rabbits' Aqueous Humor Following Intravenous Injection of E. Coli Toxin, Proc. Soc. Exper. Biol. & Med. **51**:130, 1942.

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EFFECT OF INTRAMUSCULAR ADMINISTRATION OF MORPHINE, ATROPINE, SCOPOLAMINE AND NEOSTIGMINE ON THE HUMAN EYE

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AND
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A CONSIDERABLE amount of data has been collected concerning the effects of locally administered drugs on the human eye; the indications and contraindications for the use of such drugs are well known to members of the medical profession. On the other hand, information is limited as to the effects on the eye of these same drugs when administered systemically in their usual dosage. Patients with ocular diseases, such as glaucoma, may occasionally be given morphine or atropine for the treatment of a concomitant disease. General surgeons commonly use morphine, atropine, scopolamine and neostigmine in either the preoperative or the postoperative care of patients, without definite knowledge of the effect of these drugs on incidental diseases of the eye. Morphine is said to increase the intraocular pressure when administered systemically.[1] This action would contraindicate its use in some cases of glaucoma.

Therefore, data were obtained concerning the effect of morphine on size of the pupil, accommodation and intraocular pressure in normal and in glaucomatous eyes. At the same time, information was acquired on the effect of systemically administered atropine, scopolamine and neostigmine on pupillary size and accommodation; it was not possible to measure intraocular tension in these cases.

METHOD

Twenty-five normal subjects received 8 to 18 mg. of morphine sulfate intramuscularly. Eight patients with glaucoma (3 with chronic simple glaucoma, patients 31, 32 and 33; 2 with glaucoma secondary to uveitis, patients 26 and

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1. Myashita: Zentralbl. Biochem. Bioph. **15**:95, 1913; cited by Sollmann, T.: A Manual of Pharmacology, ed. 6, Philadelphia, W. B. Saunders Company, 1943, p. 277.

TABLE 1.—*Ocular Changes Following Intramuscular Injection of Morphine Sulfate*

Subject No.	Change in Pupillary Size, Mm.		Change in Near Point, Cm.		Change in Tension, Mm.		Dose of Morphine Sulfate, Mg.
	O. D.	O. S.	O. D.	O. S.	O. D.	O. S.	
1	—2.5	—2.5	—3.5	—1.5	—3	—6	8
2	—1.0	—1.0	—2.0	—3.0	0	—1	8
3	—1.5	—1.5	—1.5	—1.5	—7	0	8
4	—1.5	—1.5	—2.5	—1.5	—3	—6	8
5	—3.0	—3.0	—	—	—3	—5	8
6	—1.0	—1.5	—	—	—1	+4.5	8
7	—2.0	—1.0	—	—	0	—2.5	8
8	—1.5	0	—	—	0	—2	8
9	—2.5	—3.0	+0.3	+0.4	—	—	8
10	—2.0	—2.0	—1.5	—2.0	—	—	8
11	—3.0	—3.0	—1.0	—1.5	—	—	8
12	*	*	—	—	—1	—2	8
Average	—1.9		—1.6		—2.2		
13	—3.0	—3.0	—1.8	—1.1	—	—	15
14	—	—	—1.0	—1.0	—	—	15
15	—2.0	—2.0	—1.0	—0.5	—	—	15
16	—2.0	—2.0	—2.5	—4.2	—	—	15
17	—5.0	—5.0	—6.5	—5.2	—	—	15
18	—4.0	—4.0	—3.7	—3.0	—	—	15
19	*	*	—	—	—5	—3	15
20	*	*	—	—	—1	—1	15
21	*	*	—	—	—1	+1	15
22	*	*	—	—	0	+1	15
23	*	*	—	—	—2	—2	15
24	*	*	—	—	—6	—5	15
25	—4.0	—4.0	—2.6	—2.0	—	—	18
Average	—3.3		—2.6		—2.0		
26	0	0	—	—	0	0	15
27	0	—	—	—	0	—	15
28	0	—	—	—	—2	—	15
29	0	0	—	—	0	0	15
30	—0.5	—1.0	—	—	—3	—2	15
31	0	—0.5	—	—	—12	—7	15
32	—1	—0.5	—	—	—10	—6	15
33	0	0	—	—	—5	—2	15
Average	—0.2				—3.5		

*The pupils were measured in bright light, being already constricted. Patients 31, 32 and 33 had chronic simple glaucoma; patients 26 and 29, glaucoma secondary to uveitis; patients 27 and 28, glaucoma secondary to intraocular growths, and patient 30, congenital glaucoma.

29; 2 with glaucoma secondary to intraocular growths, patients 27 and 28, and 1 with congenital glaucoma, patient 30) were given 15 mg. of morphine sulfate intramuscularly. Eight of the normal subjects received 0.6 mg. of atropine sulfate; 8 others received 0.4 to 0.6 mg. of scopolamine hydrobromide, and 6 others, 1.0 to 1.1 mg. of neostigmine methylsulfate, intramuscularly.

In most subjects, the pupillary size was measured before injection and repeatedly for two hours after injection. On subjects 19 to 24, who received morphine, pupillary measurements were made in a brightly sunlit ward; the pupils were constricted to 2.5 mm. or less before injection of the drug, and consequently the measurements of pupillary size were of no value. On all other patients, measurements were made in a room with constant artificial illumination. Near points of accommodation were measured with a Duane line. The intraocular tension was measured with a Schiötz tonometer before the injection of morphine and at one and two hour intervals afterward; a change of 2 mm. of mercury was considered a significant alteration in tension. The occurrence of ocular and systemic symptoms was noted in all subjects.

RESULTS

Morphine Sulfate.—Of the four drugs given systemically, morphine produced the most significant and consistent ocular effects. Even with 8 mg. (1/8 grain) doses, all subjects showed a decrease in pupillary size (average 1.9 mm.) or a shortening of the near point of accommodation (average 1.6 cm.) (table 1). These changes always began within twenty-five to forty minutes (the time of the first postinjection reading). The injection of 8 mg. of morphine sulfate (subjects 1 to 12) was followed by an increase in intraocular tension in only 1 of 18 eyes; in 13 eyes the tension fell, the average decrease being 2.2 mm.

With the usual dose of 15 to 18 mg. (1/4 grain) (subjects 13 to 25), the pupils of all subjects narrowed (average decrease, 3.3 mm.), and the near points of accommodation shortened (average, 2.6 cm). Intraocular tension rose 1 mm. of mercury (Schiötz) in 2 of the 12 eyes, but the average effect was a decrease of 2.0 mm. of mercury (Schiötz). Maximal effects were noted within one and one-half to two hours.

Fifteen milligrams of morphine sulfate was injected into 8 glaucomatous patients (26 to 33) (with tensions ranging from 28 to 65 mm. of mercury) twenty-four to thirty-six hours after all local ocular therapy had been stopped. The injection of morphine was not followed by any increase in intraocular tension in these eyes. The decreases in tension ranged from 0 to 12 mm. of mercury and averaged —3.5 mm. of mercury. Morphine did not significantly alter the intraocular pressure in any of the glaucomatous eyes except those with chronic simple glaucoma, and possibly 1 eye with congenital glaucoma. Only slight pupillary constriction occurred in the glaucomatous patients.

Atropine Sulfate.—Although each subject receiving 0.6 mg. (1/100 grain) of atropine sulfate complained of dryness of the mouth and

throat, only 3 of the 8 subjects had any mydriasis. The range in pupillary change was from 0 to +1.5 mm., the average being +0.4 mm. (table 2). A lengthening of the near point was observed in 10 of the 16 eyes;

TABLE 2.—*Ocular Changes Following Intramuscular Injection of Atropine, Scopolamine and Neostigmine*

	Change in Pupil Size		Change in Near Point	
	O. D.	O. S.	O. D.	O. S.
0.6 Mg. of Atropine Sulfate				
1	+0.5	+0.5	+1.2	—0.7
2	0	0	+2.8	+1.2
3	+1.5	+1.5	+1.7	+1.7
4	+1.0	+1.0	—0.2	+2.2
5	0	0	—0.5	+0.5
6	0	0	—0.9	—0.7
7	0	0	+1.8	+1.4
8	0	0	+0.9	—0.3
Average	+0.4		+0.8	
0.4 to 0.6 Mg. of Scopolamine Hydrobromide				
1	+1	+1	+2.2	+1.5
2	+1.5	+2	+1.8	+4.2
3	+1	+1	—2.1	—0.5
4	0	0	+0.5	—
5	+1	+1.0	+10.0	+6.6
6	+2	+2	+5.7	+4.7
7	+0.5	+0.5	+2.8	+1.3
8	+1	+1	+0.7	+1.5
Average	+1.0		+2.7	
1.0—1.1 Mg. Neostigmine Methylsulfate				
1	+0.5	+0.5	—1.2	—0.8
2	+0.5	+0.5	+0.5	+0.7
3	0	0	—1.6	—3.5
4	0	0	—0.5	+0.5
5	—1	—1	+1.5	+0.9
6	0	+0.5	—	+1.5
Average	+0.2		—0.2	

the range of changes in the near point was —0.7 to +2.8 cm., and the average was +0.8 cm. The maximal effects were noted within one to one and one-half hours.

Scopolamine Hydrobromide.—Seven of 8 patients receiving 0.4 to 0.6 mg. (1/150 to 1/100 grain) of scopolamine hydrobromide experienced mydriasis (average increase in pupillary size, 1.0 mm.). Weakening of accommodation occurred in 13 of 15 eyes (average change in near points, 2.7 cm.). Practically all the subjects complained of dryness of the mouth and vertigo, beginning within five to twenty minutes after the injection. One subject complained of blurring of vision and 2 others of ocular discomfort.

Neostigmine Methylsulfate.—The ocular effects produced by neostigmine were slight and inconsistent, though all subjects had some systemic symptoms, such as abdominal pain or twitching of skeletal muscles, appearing within an average of thirty-five minutes after the injection. Lacrimation and twitching of the eyelids occurred in 1 subject. The changes in pupillary size and accommodation were all within the limit of error of the methods.

COMMENT

The effect of morphine on the pupil is well known; this study merely confirms the observation that decided pupillary constriction follows even small doses (8 mg.) given intramuscularly. The same dose also produced definite increase in accommodative power of the eye. More important than either of these actions is the effect on intraocular tension. Though it is said that morphine produces a rise in intraocular tension, the present studies show that the characteristic effect of morphine is to lower intraocular tension. In glaucomatous patients, the only change produced by morphine was a fall in intraocular pressure. Though morphine is certainly not recommended as a therapeutic agent for any type of chronic glaucoma, it is not contraindicated in glaucomatous patients, since its only action might be a beneficial one so far as the effect on the eye is concerned. This statement, of course, does not apply to its use after ophthalmic operations, when vomiting may be disastrous. The method by which morphine lowers intraocular tension is not known. It may be through its effect on the scleral spur and ciliary muscle. As can be seen from table 1, morphine may lower the intraocular tension without increasing the miosis.

These effects of morphine are not produced by local ocular instillation but occur only after systemic absorption. The effects are said to be due to an action on the oculomotor nuclei in the brain.

It was surprising to find that atropine sulfate (0.6 mg. administered intramuscularly) produced so little effect on the eye. In slightly lower or in the same dosage, scopolamine produced much more consistent and powerful effects on pupillary size and accommodative power. The dose in all cases was sufficient to cause dryness of the mouth and throat. In the

case of patients with glaucoma undergoing surgical procedures (or otherwise requiring the systemic use of atropine or scopolamine), preference should be given to atropine because of its lesser effect on the eye. Even atropine, however, should be used with caution in such patients.

Neostigmine can be administered systemically in ordinary doses to patients with ocular disease without fear that it will produce well defined effects on the eye.

CONCLUSIONS

1. Morphine sulfate, in doses ranging from 8 to 18 mg. administered intramuscularly, produced pupillary constriction, increase in accommodative power and decrease in intraocular tension in normal eyes.

2. Morphine produced similar effects in glaucomatous eyes; in none of the 14 eyes in this study did its use lead to an increase in intraocular pressure.

3. In equivalent doses, atropine produced much less pupillary dilation and weakening of accommodation than did scopolamine (both drugs were administered intramuscularly).

4. Neostigmine, in a dosage which produced definite increase in intestinal peristalsis, had no consistent ocular effects.

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DELAYED KERATITIS DUE TO MUSTARD GAS (DICHLORODIETHYL SULFIDE BURNS)

Report of Two Cases

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NO REPORT of delayed keratitis due to mustard gas (dichlorodiethyl-sulfide) burns among United States veterans of World War I appeared in the literature until the recent review of Scholz and Woods.[1] However, many such cases have been reported in the British, French and German literature,[2] so that the condition is a well recognized entity. Goulden[3] stated that 51 men from the British army were blinded and 180 received pensions because of visual disability due to mustard gas in World War I.

There may not have been as many gas casualties in the Army of the United States as there were in the British army. However, a report[4]

Read at the Eigthy-Third Annual Meeting of the American Ophthalmological Society, Hot Springs, Va., June 5, 1947.

1. Scholz, R. O., and Woods, A. C.: Relapsing and Chronic Ocular Lesions Following Mustard Gas Burns, Arch. Ophth. **37**:137 (Feb.) 1947.

2. Mann, I., and Pullinger, B. D.; Brit. J. Ophth. **26**:503, 1942. Mann, I.: Proc. Roy. Soc. Med. **35**:236, 1942; Brit. M. J. **1**:353, 1942. Neame, H.: Proc. Roy. Soc. Med. **22**:25, 1928; Brit. J. Ophth. **29**:102, 1945. Heckford, F.: Proc. Roy. Soc. Med. **30**:949, 1937. Moore, R. F., and Heckford, F.: Brit. M. J. **1**:497, 1929. Whiting, M. H.: Proc. Roy. Soc. Med. **33**:225, 1940. de Courcy, T. L.: Brit. J. Ophth. **27**:54, 1943. Anglade, M., and Imbert, G. G.: Ypérite: Le plus redoutable des gaz de combat, Paris, LeFrancois, 1939, p. 43. Genet, L., and Delord, E.: Bull. Soc. d'opht. de Paris, 1936, p. 521; Lyon méd. **158**:216, 1936. Genet, L.: Bull. Soc. d'opht. de Paris **49**:409, 1937; Lyon méd. **160**:229, 1937. Bonnet, P.: Bull. Soc. d'opht. de Paris **51**:407, 1939. Parlange, J. A. A.: Arch. d'opht. **46**:87, 1929. Pésme, P.: ibid. **41**:278, 1924. Sourdille, G. P.: Bull. Soc. d'opht. de Paris, 1936, p. 799. Villard, H., and Dejean, C.: Arch. Soc. d. sc. méd. et biol. de Montpellier **14**:16, 1933. Weill, G.: Bull. Soc. d'opht. de Paris **51**:281, 1939. Worms, G., and Bolotte: ibid., 1926, p. 133. Worms, G.: Soc. de méd. mil. franç., Bull., Paris **20**:229, 1926. Muntsch, O.: Leitfaden der Pathologie und Therapie der Kampfgaserkrankungen, Leipzig, Georg Thieme, 1939: Cornea, p. 112. Roese, H. F.: Zentralbl. f. d. ges. Ophth. **28**:513, 1932-1933. Rohrschneider, W.: Klin. Monatsbl. f. Augenh. **99**:447, 1937.

3. Goulden, C. B.: Proc. Roy. Soc. Med. **33**:235, 1940.

4. Personal communication to the author.

from the Office of the Surgeon General of the United States Army estimates that 52,889 casualties due to mustard gas burns were admitted to hospitals. The corneas of some of these men undoubtedly were seriously affected, as were those in the 2 cases reported in this paper. These cases, however, are typical of those reported abroad, so that they add nothing to knowledge of the lesion.

The purpose of this communication is to review briefly the signs and symptoms of delayed gas keratitis, so that more cases may be recognized and the service connection of the lesions established. Lack of recognition of the condition prevents a veteran so disabled in World War I from receiving the proper consideration, as was true in the 2 cases reported here. Time passed and considerable correspondence took place before the service connection of the disability was established in these cases.

The case reported by McKellar[5] of recurring keratoconjunctivitis which developed ten months after exposure to mustard gas is often referred to. The lesion in this case should probably be considered an exacerbation of the acute stage, rather than the type referred to as delayed keratitis, which develops eight or more years after exposure to the mustard gas.

Mann and Pullinger[6] stated that many of the pathologic changes observed in cases of delayed mustard gas keratitis may be induced by agents other than mustard gas. The diagnosis rests on a combination of the nonspecific lesions with the typical vascular and degenerative changes in a definite time relationship and at a definite anatomic site. They found the lesions due to mustard gas which were produced experimentally in rabbits had a marked similarity to those that occur in the human cornea.

The most characteristic signs given by Mann and Pullinger to identify the keratitis caused by mustard gas are the ulceration of the superficial deposits of cholesterol, the peculiar varicosities and the blood islands. These signs, they stated, have not been induced in rabbits by any other means, or observed in man in conditions other than mustard gas keratitis.

Mustard gas, dichlorodiethyl sulfide, was first employed by the German army in July 1917, after which there were numerous casualties due to the gas. A beautifully illustrated description of the early effects of mustard gas on the eyes was given by Derby[7] at a meeting of this society in 1919.

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5. McKellar, J. H.: Am. J. Ophth. **3**:309, 1920.

6. Mann, I., and Pullinger, B. D.: Am. J. Ophth. **26**:1253, 1943.

7. Derby, G. S.: Tr. Am. Ophth. Soc. **17**:90, 1919; Am. J. Ophth. **49**:119, 1920.

The course is similar in all cases. After exposure to mustard gas, the action is delayed from two to six hours. The early symptom is irritation of the eyes, nose and throat, with sneezing and sometimes vomiting. The inflammation of the mucous membrane and skin increases, and may be followed by blistering. Symptoms referable to the respiratory tract increase, with severe bronchitis, and secondary pneumonit frequently develops. The severity of the ocular and general symptoms depends on the amount of exposure and the susceptibility of the individual patient.

Whiting[8] classified persons affected with mustard gas as follows: All had photophobia and blepharospasm. Class 1, comprising about 75 per cent, had comparatively mild symptoms without corneal involvement. In class 2, totaling about 15 per cent, the eyes were moderately affected; the corneas were a little roughened but did not stain. In class 3, fortunately only about 10 per cent, the eyes were severely affected, both the cornea and the conjunctiva being involved. The area of the palpebral fissure was severely burned and presented solid white edema of the conjunctiva. The epithelium of the exposed cornea, involving the lower one half or two thirds, was gray and stained with fluorescein. It is from this 10 per cent in class 3 that "delayed keratitis" developed eight or more years later. If the eyes of 10 per cent of the 50,000 mustard gas casualties admitted to hospitals of the Army of the United States were similarly affected, several thousand United States veterans might be expected to have delayed mustard gas keratitis with defective vision.

Lister[9] reported the following early pathologic changes which were observed in eyes burned with mustard gas. The corneal epithelium was denuded, with flattening of the remaining cells. The white appearance of the conjunctiva noted in the early stages of the severer burns was due to coagulation and arrest of circulation in the conjunctival vessels. The substantia propria showed round cell infiltration in some cases. Later, the appearance was reversed; the exposed area was injected, and the vessels remained permanently enlarged, while the rest of the conjunctiva appeared normal.

Phillips,[10] who collected 70 cases, called attention to the similarity of the histories of persons with delayed keratitis due to mustard gas. They were unable to open their eyes for about a week owing to the severe photophobia and blepharospasm, which was accompanied with profuse lacrimation. After being confined to the hospital four to six months or longer, they were comparatively free from symptoms for ten to fourteen

8. Whiting, M. H.: Proc. Roy. Soc. Med. **33**:225, 1940.

9. Lister, W., in Macpherson, W. G.: History of the Great War Based on Official Documents: Medical Services, Surgery of the War, London, His Majesty's Stationery Office, 1922, vol. 1.

10. Phillips, T. J.: Proc. Roy. Soc. Med. **33**:229, 1940.

years. The onset of the delayed keratitis was marked by one or all of the following symptoms: photophobia, lacrimation and failing vision. The lower third of the cornea was affected most. Superficial ulceration occurred, and the sensibility of the cornea was less than normal. Phillips described gray, branching lines in the substantia propria seen with the slit lamp; these he compared to "skate marks on fresh ice." The pale, triangular patches on either side of the cornea he spoke of as "marbling." In these patches there was absence of small conjunctival and episcleral vessels, leaving large areas of the sclera bare, and here and there was a large distended vessel, which was more tortuous as it neared the limbus and ended in a small, corkscrew-like vessel.

This brief clinical account of the condition corresponds closely with the lesions produced experimentally with mustard gas in rabbits by Mann and Pullinger,[6] who stated that "late keratitis" is a slow degenerative process, seen in man up to twenty years after exposure to mustard gas.

REPORT OF CASES

CASE 1.—D. O., aged 47 years, when seen in February 1939, had the signs and symptoms of "delayed mustard gas keratitis" well established. I had examined him in 1917, prior to his entrance into the service, and at that time his eyes were normal, with vision of 20/15 in each eye. On Oct. 4, 1918, while asleep in a cellar, a gas shell burst near him. Although he felt all right, he reported to the first-aid station, where he slept the rest of the night. On awakening in the morning, he was nauseated and found it difficult to open his eyes because of photophobia. He was hospitalized for eight months. His lungs were also affected. In 1919 I again examined him, when he said that his eyes were irritated and sensitive to light at times. Except for slight hypermetropic astigmatism, his eyes appeared normal. In 1928 a faint corneal opacity was first observed down and temporally in the left eye, and there was a faint, almost imperceptible, haze of both corneas. Photophobia had increased, but vision was still 20/15 in each eye. In February 1939 failing vision and photophobia were more pronounced, so that he wore an eye shade at his work and avoided bright light. Corrected vision was 20/25 in the right eye and 20/20 in the left eye. There was now a definite, faint, superficial haze involving the lower two thirds of each cornea, being denser in the right eye than in the left. Although the cornea was sensitive to light, the sensibility was less than normal. In October 1939, twenty-one years after he had been gassed, his symptoms had increased in severity, and his corrected vision was reduced to 20/40 in the right eye and 20/25—2 in the left eye. The corneal haze was denser in each eye, and there were striae in the substantia propria of the right eye and vertical folds in Descemet's membrane. Pale, triangular areas on either side of each cornea were now more apparent. In each eye, the triangle on the right side of the cornea was larger than that on the left. A few tortuous vessels were seen in these areas, and there were a few scattered deposits of cholesterol. The epithelium first began to break down a year later, in July 1940. The right eye was affected first, and the cornea stained in several places. There were many recurrences of the process in the right eye, with progressive degenerative changes. A heaping up of yellowish crusts of degenerated tissue on the cornea caused considerable irritation, and the lesions were removed. The vessels in the

triangles, particularly the temporal one in the right eye, became larger and more tortuous, and vision in the right eye was reduced to 20/100. On March 12, 1943, photographs (figs. 1 and 2) showed the degenerative changes to be more advanced in both eyes, and corrected vision was 6/200 in the right eye and 20/25 in the

Fig. 1 (case 1).—Right eye, showing degenerative changes in the cornea, with deposits of cholesterol and tortuous vessels in the pale, atrophic, triangular areas on either side of the cornea.

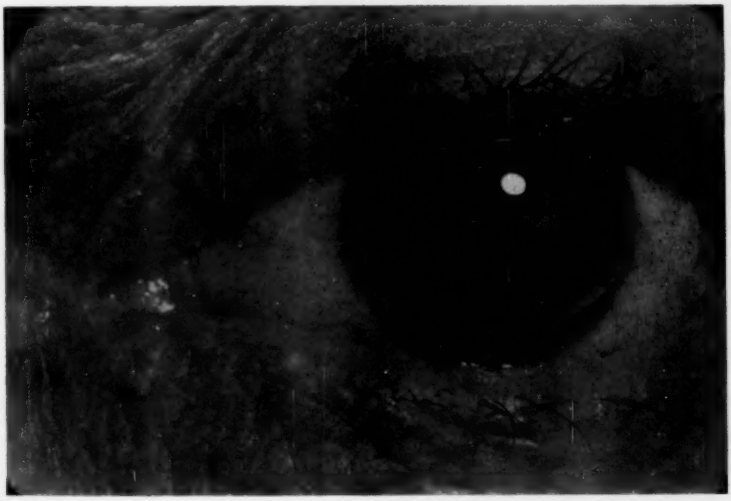

Fig. 2 (case 1).—Left eye, showing a condition similar to that in the right eye.

left eye. On Feb. 26, 1944, the vessel in the temporal triangle of the right eye was larger and more tortuous as it approached the corneal margin. Adjacent to it, in the superficial layers of the substantia propria of the cornea, was an intracorneal hemorrhage. In March 1946, corrected vision was reduced to 3/200 in

the right eye (fig. 3) and to 20/60 in the left eye. The photophobia and lacrimation were increased, but the epithelium was intact. Folds in Descemet's membrane appeared in the cornea of the left eye, and there were a few striae in the substantia propria, similar to those in the cornea of the right eye (figs. 4 and 5).

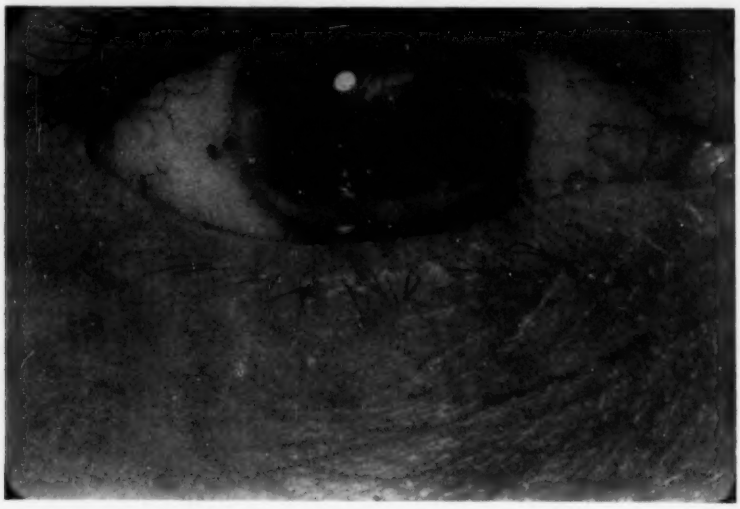

Fig. 3 (case 1).—Right eye, showing a condition more advanced than that presented in figure 2.

Fig. 4 (case 1).—Left eye, showing folds in Descemet's membrane and a few striae in the substantia propria as seen with the slit lamp.

In February 1947, there was less photophobia, and vision had improved a little in the right eye, to 20/200. This acuity was not improved with glasses. The left eye remained the same, vision being 20/60 with correction. The improvement in

vision was thought to be due to a few clear spots, where the crusts had been removed. Contact lenses were advised.

CASE 2.—R. M., aged 42, was first examined by me on May 21, 1938, twenty years after he had been exposed to a gas shell barrage. The shelling began about 11 p.m., on June 14, 1918, and he had had his mask on and off during the night. In the morning his eyes began to smart and tear and were tightly closed by the time he reached the first-aid station. He was in the hospital for about two months, and his eyes were bandaged for about a month. His lungs were also affected. After discharge from the Army, he had no ocular symptoms until a few months before he consulted me, when he noticed that the vision in his left

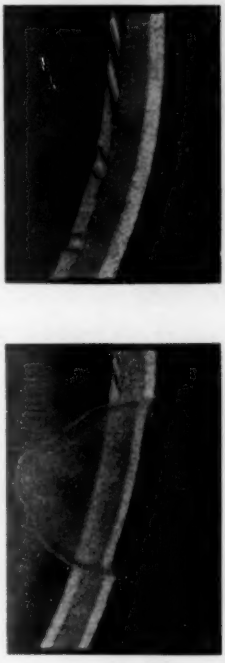

Fig. 5 (case 1).—Slit lamp beam, showing depressed area and folds in Descemet's membrane in the left eye.

eye was blurred and that there was a spot on this eye, similar to the spots which later appeared in the cornea of the right eye, and which are shown in figure 6. Vision was 20/15—2 in the right eye and 20/15—4 in the left eye. Both corneas were hazy in the area of the palpebral fissures. The haze, which somewhat resembled a lacy web, appeared to be located just under the epithelium. It was interspersed with small, irregular, white deposits, tinged yellow, with branchlike projections. Some appeared to have coalesced. The condition was more pronounced in the left eye. In each eye, pale, triangular areas were present on each side of the cornea, and in these areas were scattered a few similar yellow deposits and a few tortuous, irregularly shaped vessels. The condition progressed slowly; the deposits became larger, and more of them in the left eye coalesced to form a large, yellowish, irregular elevation (figs. 7 and 8). The sensitivity of the left

cornea was less than that of the right, but both were less sensitive than normal. The elevated patch was removed from the left cornea but many deposits were left. The patient was comfortable until the summer of 1945, when a similar elevation, which caused considerable irritation, developed on the same cornea.

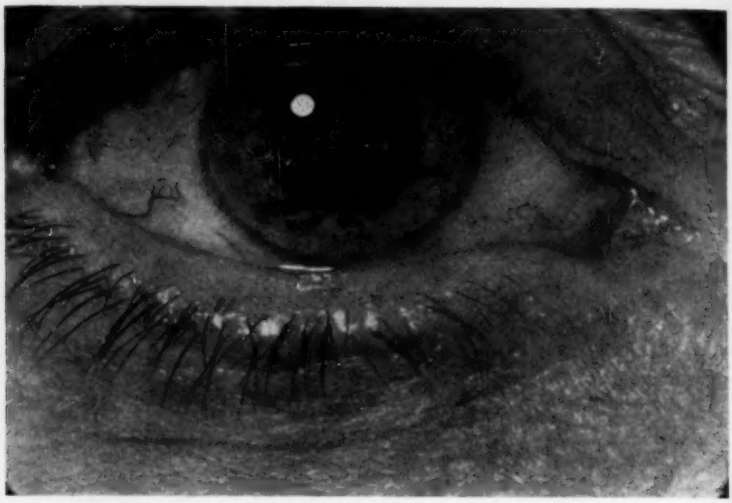

Fig. 6 (case 2).—Cornea of the right eye; early manifestations, consisting in small deposits of cholesterol in the cornea and tortuous vessels.

Fig. 7 (case 2).—Cornea of the left eye, showing a more advanced stage, with coalescence of yellow deposits and tortuous vessels.

The right cornea was a little hazier, with vision of 20/20, and in the left eye vision was reduced to 20/200. A keratectomy was done, the thin strip of cornea which contained most of the cholesterol deposits being removed. One month

after the operation his vision was 20/200, being the same as before the operation. On examination in March 1946, he stated that both eyes had been comfortable since the last examination; vision in the right eye was still 20/20, but vision in the

Fig. 8. (case 2).—Cornea of the left eye, showing further coalescence, which formed an irregular elevation of the deposits.

Fig. 9 (case 2).—Left eye, with clear horizontal band corresponding to the site of keratectomy.

left eye was reduced to 8/200, and was not improved with glasses. Both eyes were quiet, and the left eye showed a moderately clear horizontal band corresponding to the site of the keratectomy (fig. 9).

COMMENT

Late corneal lesions develop more frequently in cases with greater exposure to mustard gas and in those of greater susceptibility to it. The condition is aggravated if the eyes are bandaged during the acute stage following exposure to the mustard gas. Derby[7] mentioned a case in which both eyes were seriously affected by bandaging. Duke-Elder[11] warned against the use of bandages in the acute stage after exposure to the gas and suggested bland symptomatic treatment. It is generally conceded that active treatment in the acute stage is contradicted.

After recovery from acute symptoms, which in cases of severe burns last from two to eight months, and sometimes longer, the patient is practically free from symptoms for eight years or more.

Photophobia, lacrimation and failing vision mark the onset of the late corneal lesions. Superficial haze of the cornea just beneath the epithelium in the area of the palpebral fissure, lines or striae in the substantia propria (figs. 4 and 5) and folds in Descemet's membrane may precede the formation of deposits of cholesterol and fat. These deposits increase in size and break through the epithelium, producing an exacerbation of the symptoms of irritation. Later, there is a heaping up of hard, degenerative tissue on the cornea. As these lesions increase in size, they cause more and more irritation, until they are cast off or removed, leaving rather clear, irregular, depressed spots. The scarred cornea is so irregular that vision is improved very little with glasses. However, with contact lenses an astonishing improvement was reported by Mann.[6] In a case in which there was no improvement with glasses, vision was improved from 6/36 to 6/6 with contact lenses. In a later report, Mann[12] reviewed 84 cases of delayed gas keratitis in which the patients were fitted with contact lenses. In addition to producing great improvement in vision, acuity in 1 case being increased from counting fingers to 6/12, the lenses are tolerated well, owing to decreased sensibility of the cornea. They also afford some protection against minor injuries, and the recurrence of ulceration is less frequent. Nevertheless, a letter[13] from the regional office of the United States Veterans Administration states that contact lenses are issued only to veterans who are unable to wear ordinary frames because of wounds or scars which affect the temples or nose, and that it is unable to approve the issuance of contact lenses for veterans whose vision has been reduced by delayed mustard gas keratitis.

No reports of successful corneal transplants for this condition have been found in the literature.

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11. Duke-Elder, W. S.: Textbook of Ophthalmology, St. Louis, C. V. Mosby Company, 1938, vol. 2, p. 1714.

12. Mann, I.: Brit. J. Ophth. **28**:441, 1944.

13. Personal communication to the author.

Other important diagnostic signs are pale, triangular, atrophic-looking patches on either side of the cornea in the area of the palpebral fissures. In the triangles there is absence of conjunctival and episcleral vessels, with an occasional vessel distended, of tortuous, varicose type. There are also a few scattered deposits of cholesterol. These areas have somewhat the appearance of lesions produced by surface application of beta radiation. Intracorneal hemorrhages occur and appear to arise from the large varicose vessels, which extend up to the limbus.

CONCLUSION

Recognition of the late effects of mustard gas on the cornea is important in order to establish the service connection of the disability, so that claims of veterans, so disabled in World War I, may be justly handled

Dr. James E. McAskill made the photographs in these cases.

129 Clinton Street.

TREATMENT OF OCULAR SYPHILIS WITH PENICILLIN

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Although penicillin has been extensively employed in the treatment of various syphilitic infections, only a few reports have been made evaluating its use in ocular syphilis.[1] During the past three years we have used penicillin in the treatment of 39 patients with various manifestations of syphilis of the eye. The results are presented in this report.

INTERSTITIAL KERATITIS

The efficacy of any form of therapy for interstitial keratitis must be considered in the light of the natural course of this infection. Untreated syphilitic interstitial keratitis involves both eyes in the majority of cases.[2] Involvement of the second eye may occur from weeks to years after that of the first and may lead to functional blindness (vision less than 20/200). The usefulness of one eye is lost in almost 20 per cent of untreated patients and that of both eyes in 6 per cent.[2a] According to Klauder and Van Doren,[3] 35 per cent of untreated patients with interstitial keratitis retain good to excellent vision (20/70 to 20/20) in the poorer eye. Other reports show that 28 to 40 per cent of untreated

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This study was aided by a grant from the United States Public Health Service.

From the Departments of Ophthalmology and Medicine of Grady Hospital and Emory University School of Medicine, and the Georgia Department of Public Health.

1. *(a)* Klauder, J. V., and Dublin, G. J.: Syphilitic Uveitis: Diagnosis, Herxheimer Reaction and Results of Various Treatments, Including Penicillin Therapy, Arch. Ophth. **35**:384 (April) 1946. *(b)* Moore, J. E.: Penicillin in Syphilis, Springfield, Ill., Charles C Thomas, Publisher, 1946. *(c)* Stokes, J. H.; Steiger, H. P., and others: Penicillin Alone in Neurosyphilis, J.A.M.A. **131**:1 (May 4) 1946.

2. *(a)* Moore, J. E.: The Modern Treatment of Syphilis, Springfield, Ill., Charles C Thomas, Publisher, 1943. *(b)* Woods, A. C.: Syphilis of the Eye, Am. J. Syph., Gonor. & Ven. Dis. **27**:133, 1943.

3. Klauder, J. V., and Van Doren, E.: Interstitial Keratitis: Analysis of Five Hundred and Thirty-Two Cases, with Particular Reference to the Standardization of Treatment, Ven. Dis. Inform. **22**:307, 1941; Arch. Ophth. **26**:408 (Sept.) 1941.

patients have a final visual acuity of 20/30 or better.[4] Any form of treatment must, of course, show results superior to these before it can be considered of value.

Case Material and Procedures.—In this study 15 patients were treated for acute active interstitial keratitis. Three of these patients had had previous episodes of keratitis. The remaining 12 had interstitial keratitis for the first time. Four of these 12 patients were treated on two different occasions for keratitis of first one eye and then the other. The keratitis was considered to be severe or moderately severe in all but 1 of the 15 patients. Thirteen of the patients were Negroes; 2 were white persons. Eleven were female and 4 male. All the patients were thought to have congenital syphilis; none of them had other clinical evidence of an active infection. Quantitative Kahn titers before treatment ranged from 40 to 640 units. Examination of the spinal fluid revealed no evidence of syphilis in any case.

The ages of our patients varied from 6 to 26 years. Eight of the patients were 15 years of age or less. One patient had received previous treatment for syphilis with 2,400,000 units of penicillin six months before the development of interstitial keratitis, while 2 other patients had received a total of ten and thirty injections, respectively, of arsenical and bismuth preparations several years previously. The 3 patients treated for recurrence of their keratitis had received inadequate arsenical and bismuth therapy for their initial keratitis.

In this study, treatment of the keratitis in 5 of the 7 adults consisted of 4,000,000 units of commercial penicillin given in doses of 50,000 units intramuscularly every three hours for ten days. One patient received a total of 2,000,000 units, and another a total of 3,000,000 units. Early in this study the children were given a total dose of 50,000 units of penicillin per kilogram of body weight. This dose was subsequently increased to 100,000 units per kilogram of body weight. Six of the patients who showed no response to penicillin at the completion of treatment were given fever therapy with typhoid vaccine. Three of these 6 patients had recurrent interstitial keratitis. Three patients treated early in this study also received approximately fifteen injections of oxophenarsine hydrochloride U.S.P. and ten injections of a bismuth preparation immediately after penicillin therapy.

Local treatment was given each patient and consisted in complete and prolonged atropinization, use of hot compresses and, in some instances, local instillation of penicillin solution into the eye. The last measure did not appear to increase the effectiveness of the treatment and was used in only a few cases. Local treatment was continued until all the ciliary injection or photophobia was relieved. This often occurred several weeks after penicillin had been completed. After discharge from the hospital, patients were instructed to return every two weeks until the active process had subsided, and then every three or six months. All the patients were observed for at least eight months; 3, from one to two years, and 3, for more than two years.

Results.—A total of 20 eyes were treated for the initial infection and 4 eyes for recurrent infection. The final visual acuity for the group with the initial infection eight months to two years after treatment is shown in table 1.

It should be noted that 16, or 80 per cent, of the 20 eyes treated for initial involvement finally showed good to excellent vision. The effect

4. *(a)* Carvill, M., and Derby, G. A.: Interstitial Keratitis, Boston M. & S. J. **193**:403, 1925. *(b)* Dennie, C. C., and Pakula, S. F.: Congenital Syphilis, Philadelphia, Lea & Febiger, 1940. *(c)* Cole, H. N., and others: Late Prenatal Syphilis, with Special Reference to Interstitial Keratitis: Its Prevention and Treatment, Arch. Dermat. & Syph. **35**:563 (April) 1937. Ven. Dis. Inform. **18**:97, 1937.

of penicillin treatment, however, was rarely apparent during the period of treatment. Almost all the patients showed as much or more inflammatory reaction at the completion of the ten day treatment as at the beginning. Only 1 patient showed marked improvement during penicillin therapy, and the keratitis recurred in the other eye two weeks later. In 7 of the patients the vision was so impaired at the completion of penicillin treatment that they could not count fingers at a distance greater than 2 feet (60 cm.). Without further treatment the keratitis cleared satisfactorily in three to five months, and 5 of these 7 patients obtained good to excellent vision. The appearance of the eye at the completion of penicillin treatment apparently does not indicate the amount of corneal clearing that may finally result.

TABLE 1.—*Vision Obtained After Treatment in Cases of Initial Infection*

	No. of Patients Treated	No. of Eyes Treated	Number of Eyes Obtaining Specified Visual Acuity			
			Excellent 20/20-20/30	Good 20/40-20/70	Poor 20/100-20/200	Bad 20/200
Penicillin alone	9	16	7	8	1	0
Penicillin and fever	3	4	1	0	2	1
Total	12	20	8 (40%)	8 (40%)	3 (15%)	1 (5%)

Although early in this study fever therapy was given to those patients who failed to respond to penicillin, this additional treatment may not be necessary, since we have found that some of the most severely involved eyes will clear after the use of penicillin alone if observed for a sufficient period.

Of the 4 eyes treated for recurrent interstitial keratitis, 3 had a final visual acuity of 20/200 or less. The remaining eye had 20/100 vision. As was to be expected, the results in these eyes were worse than in those treated for the initial lesion.

Comment.—In this series of 15 patients with interstitial keratitis treated with penicillin either alone or combined with artificial fever, not less than 14 obtained good to excellent vision in one or both eyes. Only 1 patient continued to have poor vision in both eyes, and this patient was treated for recurrent keratitis. In general, our results are similar to those obtained by Klauder and his associates,[5] who used penicillin in 55 cases gathered from various clinics. Only 16 of their patients were treated with penicillin alone; the others apparently had a severer infection and received fever therapy in addition to penicillin. Seventy-one per cent of the patients in their study obtained good (20/50 or better) vision.

Penicillin therapy may not prevent involvement of the second eye. Although none of our patients has thus far had recurrence of keratitis in the same eye after penicillin therapy, 1 of them had been given penicillin for latent syphilis six months before her keratitis developed. In another patient, not included in the present series, but previously re-

5. Klauder, J. V., cited by Moore.[1b]

ported on,[6] keratitis developed two weeks after the administration of penicillin for Clutton's arthritis.

These observations, together with the fact that penicillin produced little or no immediate effect on the keratitis, suggests that the course of this condition may not be altered by penicillin therapy. It is obvious that a much larger series of patients should be treated with penicillin before the usefulness of this drug can be accurately evaluated.

Despite these reservations, the results obtained with this small series of patients appear to be better than those obtained with older methods of therapy. The use of routine arsenical and bismuth preparations has been shown to give "satisfactory" results in only 65 per cent of a large series of cases,[7] whereas the addition of fever therapy resulted in good to excellent vision in approximately 55 per cent.[8] The use of penicillin for this condition has certain additional advantages in that it not only acts on the underlying systemic infection but is also nontoxic and does not require a prolonged course of treatment.

The results presented here are better than those which were reported in a preliminary paper on some of this same group of patients.[6] This improvement is due to the fact that considerable restoration of vision comes with longer periods of observation.

Interstitial keratitis remains a difficult disease to treat satisfactorily. Woods and Chesney[9] attributed this refractoriness to treatment to the low concentration of the drug obtained in the avascular cornea. They stated that when penicillin is brought to the cornea in high concentration by iontophoresis rapid healing of the lesion takes place without vascularization. We have not had any experience with this form of therapy.

IRITIS

Inflammation of the iris occurs predominantly in the secondary stage of syphilis and usually responds satisfactorily to antisyphilitic and local treatment.

We have treated with penicillin alone 6 patients with secondary syphilis and iritis. The dosage varied from 2,400,000 to 4,000,000 units, given in equally divided amounts intramuscularly every three hours for seven to ten days. Atropine was used locally in addition to intramuscular injection of penicillin. No attempt was made to prevent a Herx-

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6. Yampolsky, J., and Heyman, A.: Penicillin in the Treatment of Syphilis in Children, J.A.M.A. **132**:368 (Oct. 19) 1946.

7. Moore.[2a] Klauder and Van Doren.[3] Cole and others.[4c]

8. Carvill and Derby.[4a] Dennie and Pakula.[4b]

9. Woods, A. C., and Chesney, A. M.: Relation of the Eye to Immunity in Syphilis, with Special Reference to the Pathogenesis of Interstitial Keratitis, Am. J. Ophth. **29**:389, 1946.

heimer reaction, and none was observed by gross examination in any patient. Three of these patients had unilateral iritis and 3, bilateral. Two had the nodular type. All 6 patients improved rapidly and obtained a final visual acuity of 20/20 in each eye; there were no complications. All these patients also showed striking improvement in their cutaneous manifestations of secondary syphilis and their serologic tests for syphilis have thus far given satisfactory responses.

Klauder and Dublin also obtained good results with the penicillin treatment of this type of iritis.[10] They treated 24 patients, the total dose being 2,400,000 units of penicillin. A Herxheimer reaction was observed either grossly or with the slit lamp in every one of their patients. The results were excellent, and normal vision was obtained in all but 1, a patient who had complete bilateral pupillary occlusion and secondary glaucoma in one eye before treatment.

In addition, we have treated with penicillin 3 patients who had iritis associated with late syphilis. One of these patients had seclusion of the pupil with complicated cataract; the second had a blind eye from previously untreated iritis, and the third had secondary glaucoma. Only the first of these 3 patients appeared to respond to treatment. No significant changes were noted in the other 2 patients.

It is often impossible to determine whether the iritis which occurs in patients with late syphilis is of syphilitic origin. The iritis in our patients may not have been related to their syphilitic infection, and the fact that 2 of them failed to respond to penicillin does not necessarily indicate that the drug is ineffective in treatment of iritis caused by late syphilis.

CHOKED DISK

Swelling of the optic nerve is often associated with acute syphilitic meningitis.[2b] This condition may simulate optic neuritis but differs in that there is relatively little impairment of vision. The swelling is probably due to increased intracranial pressure and hyperemia of the disk. Such a condition usually responds satisfactorily to arsenical and bismuth therapy.

We have treated 3 patients with acute syphilitic meningitis who had bilateral papilledema of 1 to 4 D. No disturbance of vision or constriction of visual fields was noted in 2 of these patients. The third patient had slight visual impairment and constriction of the visual fields. This patient had prominent papilledema and was thought at first to have a cerebral tumor. All 3 patients received 4,000,000 units of sodium penicillin intramuscularly, in equally divided doses every three hours for ten days. All showed satisfactory subsidence of the papilledema and relief of the meningeal symptoms. No Herxheimer reaction was noted.

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10. Klauder and Dublin.[1a] Klauder.[5]

The patient who had impaired vision before treatment obtained normal vision shortly after treatment was completed. The spinal fluid and serologic tests have likewise responded satisfactorily to penicillin therapy.

PRIMARY ATROPHY OF THE OPTIC NERVE

In the treatment of syphilitic primary atrophy of the optic nerve, arrest of the process is generally considered a satisfactory result. Little or no improvement in visual acuity or the visual fields can be expected after treatment of this condition, since the lesion is usually degenerative and irreversible changes in the optic nerve fibers have usually occurred before treatment is begun. When untreated, 70 per cent of patients with primary optic nerve atrophy are blind in three years, 90 per cent in five years and almost all within seven to nine years.[2b] Several factors are known to influence the prognosis of this condition. In general, patients with unilateral involvement, or patients with bilateral involvement who have good vision in one or both eyes, have a favorable prognosis. The outcome is bad, however, when the vision in the better eye is 20/60 or less.[2a] It should also be borne in mind that many cases of atrophy of the optic nerve have become stationary before treatment is begun and that the efficacy of a new method of treatment can be evaluated only in those cases in which the process is known to be progressive. Moreover, an observation period of at least three years is essential before definite conclusions can be drawn as to the success of treatment.

Case Material and Procedures.—There were 12 patients in this study with progressively decreasing vision caused by syphilitic primary atrophy of the optic nerve. In all these patients the spinal fluid showed strongly positive evidence of syphilis, with increased cells and protein, in addition to a positive Wassermann reaction. Eight had received previous treatment for syphilis, consisting usually of inadequate amounts of heavy metals many years before the development of their optic nerve atrophy. One patient (case 8) had received fifty-four hours of fever therapy at temperatures greater than 103F. with typhoid vaccine one year prior to the present admission, but had continued to show progression of the optic nerve atrophy and changes in the spinal fluid. Another patient (case 5) had received 1,200,000 units of penicillin two years previously for what was thought at that time to be asymptomatic neurosyphilis with amblyopia caused by tryparsamide. This patient, likewise, had pronounced diminution of vision several months prior to the present admission. All the patients showed definite pallor of the optic disk, decreased visual acuity and constriction of the fields in one or both eyes. Penicillin was given intramuscularly in doses of approximately 50,000 units every three hours for seven to sixteen days, for total doses of 2,400,000 to 6,000,000 units. Four of the patients received fever therapy in addition to penicillin, while the remaining 8 patients received penicillin alone. No other antisyphilitic treatment was employed, and the patients were instructed to return every three months for follow-up observation.

Results.—The results obtained with these patients are summarized in table 2. It will be observed that 6 of the 12 patients showed progres-

sion of their optic nerve atrophy six months to two years after treatment. Of the 8 patients treated with penicillin alone, 4 showed apparent arrest of the process. Three of these 4 patients (cases 1, 2 and 9) had moderately severe and recently progressive atrophy of the optic nerve prior to treatment. The other patient (case 3) had had symptoms for four years and might have had a spontaneous arrest, since Moore[2a] has shown that patients not blind at the end of three years usually do well even in the absence of treatment. The period of observation following treatment for these patients is relatively short, and further progression may ultimately occur.

In 6 of our patients the condition progressed to practical blindness. All had had useful vision in one eye before treatment. One of these patients (case 7) received only 2,400,000 units of penicillin, an amount now considered inadequate. This patient had severe hypertension and aortic insufficiency, and fever therapy was contraindicated. This patient has been retreated in another clinic and received 6,000,000 units of penicillin in beeswax together with eight injections of oxyphenarsine hydrochloride and five injections of a bismuth preparation. Examination two years later revealed no further loss of vision. In 2 other patients the atrophy progressed despite penicillin and malarial fever therapy.

No Herxheimer reactions were encountered in these 12 patients, even though large doses of penicillin were given to most of them throughout the entire course of therapy. In 1 patient, not included in this series, however, a severe Herxheimer reaction apparently developed, and he became completely blind after penicillin and malarial therapy.

Regardless of the response of the vision, all the patients showed a satisfactory or improved condition of the spinal fluid six months to a year after penicillin treatment.

Comment.—The results obtained in this series with the use of penicillin in the treatment of optic nerve atrophy are comparable to those obtained by other authors. Klauder[5] treated 20 patients with progressive atrophy of the optic nerve with penicillin alone in doses of 4,200,000 units. The condition of 10 of these patients remained stationary throughout observation periods of one to twenty-one months, while that of the remaining 10 patients continued to progress. Six of the latter patients had less than 20/200 vision at the onset of therapy, and deterioration would probably have progressed with any form of treatment. Stokes and his associates[1c] reported the results obtained with penicillin alone in 9 patients with presumably progressive atrophy of the optic nerve. One of their patients became blind; 4 showed further contraction of the visual fields, and 4 showed no change. Improvement in the spinal fluid was noted in almost all their patients despite progression of the ocular process. Another group of 15 patients with atrophy of

TABLE 2.—*Summary of Data on 12 Patients with Atrophy of the Optic Nerve Treated with Penicillin*

Patient No.	Age	Race	Sex	Duration of Visual Impairment, in Months	Visual Acuity Before Treatment		Dose of Penicillin, Units	Additional Treatment	Months Observed After Treatment	Visual Acuity After Treatment		Final Status
					Right	Left				Right	Left	
1	42	N	F	8	Light perception	20/70	5,800,000	None	25	Light perception	20/70	Stationary
2	42	N	M	8	8/200	20/50	6,000,000	None	24	8/200	15/70	Stationary
3	47	N	M	48	20/30	Light Perception	5,400,000	None	25	20/30	Light perception	Stationary
4	35	N	M	1	20/25	20/30	4,000,000	Typhoid Vaccine	23	20/25	20/25	Stationary
5	44	W	F	24	20/20	Blind	6,000,000	Malaria	18	20/20	Blind	Stationary
6	40	N	M	8	Light perception	20/70	4,800,000	Malaria	21	Light perception	Finger perception	Progressed
7	58	N	M	6	10/200	20/100	2,400,000	None	41	Light perception	5/200	Progressed
8	38	N	F	24	20/100	20/200	5,300,000	None	23	20/200	Light perception	Progressed
9	63	N	M	12	20/50	20/100	4,800,000	None	11	20/100	20/100	Stationary
10	36	N	M	12	20/70	20/100	6,000,000	None	19	20/100	20/100	Progressed
11	31	N	F	3	20/100	1/200	4,800,000	Malaria	13	Light perception	Blind	Progressed
12	55	N	F	12	20/50	Light perception	4,800,000	None	11	8/200	Light perception	Stationary

the optic nerve were treated by Curtis and his co-workers.[11] Four of their patients received penicillin alone; 11 had induced malaria fever in addition. Only 2 patients in their series showed diminution of vision, and these patients had received the combined treatment.

It is difficult to draw definite conclusions as to the value of penicillin in these small series of patients, many of whom have been observed for short periods. It would appear from the foregoing studies, however, that the use of penicillin alone is effective in arresting the process in approximately one-half the cases. Since malaria therapy has been shown to be valuable in the treatment of this condition, the use of penicillin alone is not advisable, and a combination of penicillin and fever therapy is probably the treatment of choice. In patients who cannot tolerate fever, however, penicillin is indicated and is superior to other forms of chemotherapy.

CONCLUSIONS

The results obtained with the use of penicillin in the treatment of various forms of syphilis of the eye are reported. Penicillin produced little or no immediate response in patients with interstitial keratitis. Clearing of the opacity and subsidence of the inflammation, however, occurred in most patients three to five months after penicillin therapy. Good to excellent vision was finally obtained in 80 per cent of the eyes treated for the initial involvement. Penicillin did not prevent involvement of the second eye in several of our patients, nor did it prevent the appearance of keratitis in 1 patient when given previously for latent syphilis.

Penicillin treatment of 6 patients with acute iritis associated with secondary syphilis resulted in immediate healing of the process and restoration of vision to normal.

Papilledema associated with syphilitic meningitis responded well to penicillin therapy with subsidence of edema and return of normal vision. Eight patients with primary atrophy of the optic nerve were treated with penicillin alone. Four obtained apparent arrest of the process eleven months to two years after completion of treatment.

In general, penicillin appears to be of value in the treatment not only of systemic syphilis but also of the ocular manifestations of this disease. It should be used in combination with fever therapy for atrophy of the optic nerve, but satisfactory results were obtained with penicillin alone in treatment of the other forms of ocular syphilis.

Fort Lauderdale, Fla. (Dr. Benton).
36 Butler Street (3) (Dr. Heyman).

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DIAGNOSIS OF RETINOBLASTOMA

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Retinoblastoma is an intriguing subject because of the difficulty of early diagnosis, the fearful penalty for delay in treatment, the question of hereditary transmission and the implications of birth control in the affected families. For these and other reasons, the subject of retinoblastoma is presented in the clinical form of 6 case histories, with a description of the ocular signs which led to enucleation in 5 cases and in the sixth, to the unmistakable diagnosis of angiomatosis.

Considering the frequency with which an acute inflammatory reaction leaves a yellow pupillary reflex, which is recognized as the primary sign of retinoblastoma, it is no wonder that eyes are sacrificed; yet, as shown in case 1, the malignant disease may be ushered in by acute congestion of the bulbar conjunctiva, more suggestive of an inflammatory than of a malignant process.

REPORT OF CASES

CASE 1.—When J. K. was 3 years old she was brought to me with a history that two months before the left eye had become pink and she had been examined under ether anesthesia but that no advice or opinion had been given or treatment instituted.

When I first saw her, the right eye appeared normal on external and ophthalmoscopic examination.

The left eyeball was congested; the pupil measured 6 mm. and was stationary. The details of the iris were obscured, and there was a dull yellow pupillary reflex from a large yellow mass in the fundus, over which the vessels could be traced. The appearance was typical of retinoblastoma, and the eye was enucleated the following day. There were no gross changes in the optic nerve. The globe measured 22 by 21 mm.

Healing was uneventful, and the child was healthy and happy until three months later, when the left eyelids became edematous and puffy, with an evident local orbital swelling. This condition was controlled for a time with roentgen treatments. Four months after the first sign of recurrence the swollen eyelids became ecchymotic. This infiltration of the lids with blood never disappeared. There were no changes in the orbital bones, but the tumor steadily increased in size, becoming a large, vascularized mass. The child died one year after the first signs of the tumor.

Specimen.—Section revealed that the angle of the anterior chamber was obliterated. The posterior surface of the lens was covered by a soft, gray layer, several millimeters

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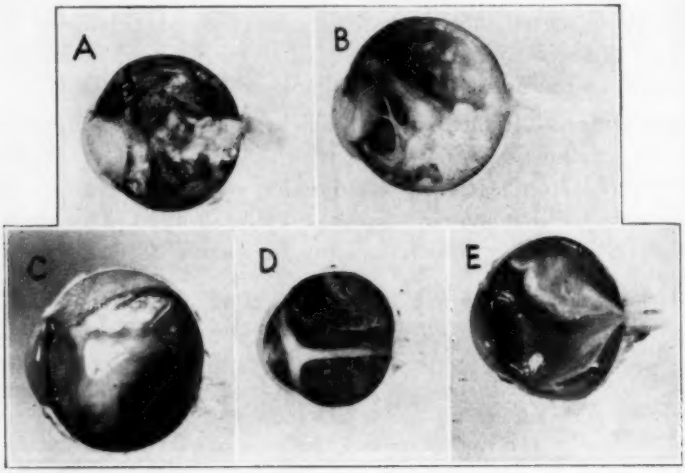
thick. The retina was transformed into a fungating mass, projecting forward 10 mm. from the papilla (figure, *A*). This mass was soft and yellow gray, with many vessels on it. There was pronounced atrophy of the ciliary processes and of the retina and choroid near the ora serrata.

Microscopically, the tumor was necrotic, with distorted remains of the retina and a delicate vascular stroma, containing dilated capillaries. The tumor cells ranged from ovoid to oat shaped, with relatively large, hyperchromatic nuclei and scanty cytoplasm. The tumor had a perivascular arrangement, which showed a slight tendency to formation of pseudo rosettes. An occasional multinucleated tumor giant cell was noted.

The diagnosis was retinoblastoma.

The case was of interest because of the early inflammatory reaction, which led the parents to delay in bringing the child for diagnosis. With



A (case 1), gross specimen of retinoblastoma, showing the fungating mass projecting from the papilla; *B* (case 2), gross specimen, showing the widespread retinoblastoma; *C* (case 3), gross specimen of leukosarcoma, showing a dense, homogeneous tumor above and a soft, flocculent mass below; *D* (case 4), gross specimen of retrolental fibroplasia with extensive intraocular hemorrhage; *E* (case 6), gross specimen of Coats's disease, showing complete detachment of the retina, with a large, thick, yellow infiltration of the retina.

a tumor of such rapid growth, it is doubtful whether anything could have prevented the fatal outcome.

CASE 2.—The slower rate of growth and the absence as yet of recurrence is illustrated in this case. The child was first seen when she was 26 months old because something was wrong with the left eye. Nine months before the parents had noticed that the left pupil had a peculiar yellow color, and lately they had noted that the eye rolled about as though she could not see. The child seemed to be in good health and was well nourished.

The right eye was normal.

The pupil of the left eye was 1 mm. larger than that of the right eye, which measured 4 mm. The vessels of the iris were full and prominent, and from the pupil there was a distinct yellow glare. The vitreous was filled with a great tangle of bright shreds. No view of the fundus was possible.

The eye was enucleated. Healing was uneventful, and up to the time of this report, four years later, there has been no recurrence of the tumor.

Specimen.—The eyeball was 24 mm. in length and 24 mm. in width and was grossly distended in the anterior half. On transillumination, most of the posterior half was dark.

On section, the anterior chamber appeared shallow; a film of cells covered the posterior surface of the lens and continued as filaments back to the tumor. The sclera was thin. The tumor was a large, cuplike, nodular, yellow mass, varying in thickness from 8 to 3 mm., growing in and on the retina, which was not detached. The optic nerve was not involved.

Microscopic sections showed a cellular tumor arising from the retina and projecting forward into the posterior chamber. The tumor was composed of spindle-shaped to oat-shaped cells with relatively large nuclei and scanty cytoplasm. The cells were loosely arranged, and there was little stroma. A moderate number of capillaries were present. In places, the cells were in palisade arrangement, and in others they tended to form spaces, or pseudo rosettes. Mitoses were infrequent.

The diagnosis was retinoblastoma.

In this case the tumor was large and was growing rapidly in and on the retina. Now, at the end of four years there has been no metastases or recurrence, so that the outcome seems favorable.

CASE 3.—A healthy-appearing boy, aged 8, had as his only complaint a boil on the left eyebrow two weeks ago.

Examination of the right eye revealed a normal condition, with vision of 6/6 and a total refractive error of +0.75 sph. +0.75 cyl., axis 90.

Vision in the left eye was 6/30. The pupil measured 3 mm. and was regular and active. There were many fine, dustlike cells in the vitreous. The disk was slightly oval, but even under the powerful light of the camera it could not be sharply outlined. The veins of the upper half of the fundus were larger than normal, and the superior temporal branch was beaded. The veins in the lower portion were not remarkable. Many reflexes were obtained from the posterior surface of the vitreous. Near the macular region was a yellow, rather sharply defined, irregular, soft, flat area, over which a dilated artery, twice its normal size, passed obliquely down and out. The appearance of the distended vein suggested that usually present in angiomatosis, although no angioma was observed. The soft, yellow area was suggestive of a growth. Palliative measures were taken. No shadow was present on transillumination.

A short time later, the child complained of pain and on examination vision was 6/120 in the left eye, with considerable photophobia. There was an area of hypopyon-like sediment, measuring 1 mm., in the anterior chamber, one bright spot on the nasal side of the pupillary edge of the iris, a larger yellow area behind the iris and a collection of cells on the anterior capsule. The sediment was so fluid that it moved easily on the least motion of the globe. The vitreous was partly filled with a soft, yellow-appearing, somewhat translucent fluid.

The visual field was small, with a large central scotoma.

The eye was enucleated. Transillumination revealed a large, dense shadow, 14 mm. at its widest portion, extending backward 15 mm. from the upper portion of the limbus.

Specimen.—On section, the growth which was between the retina and the sclera appeared yellowish gray and homogeneous, measuring 4.5 mm. at its thickest part. There was a large, soft, white-yellow mass in the vitreous, part of, and continuous with, the tumor and loosely attached to it. A1 mm. ring of pigmentation surrounded the disk.

Microscopic study of a section through the tumor extending posteriorly from the ciliary body showed that it replaced the choroid. A segment of atrophic retina overlay

the tumor. The tumor was composed of short, plump, spindle-shaped cells with large hyperchromatic muclei, which occasionally exhibited mitosis. The cells were closely packed but in places appeared to be in columns, a pseudoacinous arrangement. The later structure suggested the rosette formation of retinoblastoma. Occasional cells contained brown granular pigment. The production of pigment and the location of the tumor in the choroid made the diagnosis of melanosarcoma quite certain. Because little pigment was being produced, the descriptive term "leukosarcoma" or "a melanotic melanosarcoma" might be applied.

The diagnosis was leukosarcoma of the choroid.

Subsequent Course.—The boy remained healthy, without evident symptoms, for three months, at which time a large swelling appeared on the right and another on the left side of the lower jaw. In the region of the latter there was a large, open ulcerating area in the mouth. At the time of writing, the new growths are rapidly enlarging, and the boy has the color of approaching death.[1]

This case is of unusual interest in the appearance of the vessels, which resembled angiomatosis; the fundus picture, which suggested a growth; the pathologic type of the tumor, and the development of multiple metastases.

CASE 4.—The patient was a 4 month old girl, born in the sixth month of pregnancy. For a few weeks prior to consultation, the mother had noted that the left eye was larger than the right and that the baby did not seem to notice things as her two sisters had done at her age.

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1. The patient died five weeks after this report was made.

The anterior chamber of the right eye was shallow. The iris was dark, with a deep yellow-gray reflex visible through the pupil, which measured 3 mm. The pupil of the left eye measured 3.5 mm. and the cornea 11 mm.; the anterior chamber was very shallow, with the same gray-yellow pupillary reflex as that noted in the right eye. The parents were told that the baby was blind as a result of failure of absorption of a membrane, the fibrovascular sheath of the lens, i.e., retrolental fibroplasia.

Six weeks later the left eye had further increased in size, and enucleation was advised. The globe was removed and a glass ball implanted in the capsule of Tenon. Healing was normal. The globe was 17.5 mm. in length.

Specimen.—On section, the diagnosis of retrolental fibroplasia was verified, and the cause of the increasing size of the globe was observed to be a large subretinal hemorrhage, extending as a broad red band from the back to the choroid. The anterior chamber was abolished. There was a large anterior corticocapsular cataract. The lens was covered by a firm white membrane, 1.5 mm. in thickness, which extended back, as a white band 1 mm. in width, to the disk. The retina was completely detached.

Microscopically, the red mass consisted of coagulated vitreous with intermingled erythrocytes, without tumor cells.

CASE 5.—This case, which is without pathologic report, is presented, through the courtesy of Dr. Arthur C. Glover, to emphasize the changes observed in case 6. The diagnosis of angiomatosis seems unmistakable, and the changes characteristic of this condition, of a bizarre type, were well shown except for the angioma itself, which was outside the photographic field, in the extreme field visible with the ophthalmoscope.

The right eye was normal. The pupil measured 3.5 mm. and was regular and active. The media were clear. The disk was clearly and distinctly outlined, with a small central excavation. The vessels of the fundus were of normal size and distribution.

The pupil of the left eye measured 3 mm. and was regular and active. After instillation of atropine, the pupil was regular and dilated to 7 mm. with a +2 D. lens;

a large detachment of the retina was outlined, with a sharp, distinct edge, in the lower outer quadrant. The vessels over it gave no reflex. There were several retinal exudates, mostly circumpapillary, consisting of deposits of the circinate type. On the lower outer quadrant above the detachment, the exudate was in yellowish sheets. The disk was outlined with difficulty. The retinal arteries were slightly fuller than normal, and the veins were definitely dilated. About 2 disk diameters to the temporal side of the disk the retinal vessels converged to a point which suggested in form and color a second papilla because it was darker than the surrounding exudate. An angioma was clearly and easily seen far to the temporal side, at axis 180, when the patient looked to the extreme left.

CASE 6—An 8 month old baby did not see as well as the other children, according to the parents. He was born at full term, with a normal delivery, and had had no illnesses.

The pupils measured 3 mm. and were regular and active. After instillation of atropine, the pupils measured 6 mm.; the iris, lens and vitreous appeared normal in each eye, and with a +6 D. lens the disk was faintly visible.

The baby was not seen again for one year, when he was brought to me because of a yellow light from the pupils. A large, deep, yellow glare came from the temporal half of the fundus of each eye. The nasal side was a normal pink.

With the child under ether anesthesia, this reflex was found to be produced by a smooth-surfaced, large, yellow layer without definite boundaries but limited mainly to the temporal half of the retina.

Unfortunately, a year later the right eye became red and painful. The iris was adherent below, and the eyeball was intensely congested, with a great increase in intraocular tension.

Enucleation was done because the eyeball was obviously extensively involved and sightless and all previous treatment had been unavailing. Healing was normal, and the child has remained in good health for three years.

The left eye is unchanged; the yellow layer persists unaltered.

Specimen.—The right eyeball was 20 mm. long. The retina was completely detached and appeared as a yellow gray, uneven sheet, with many folds.

The pathologic diagnosis, made by Dr. Georgiana Theobald, was that of Coats's disease. The microscopic report follows.

"Slight round cell infiltration (lymphocytes and plasma cells) was present about the conjunctival and episcleral vessels. The cornea appeared normal except for slight round cell infiltration just anterior to the trabeclum and Descemet's membrane. The trabeculae (pectinate ligament) were compressed and contained round cells.

"Anterior Chamber: The angles were obliterated by the root of the iris.

"Iris and Ciliary Body: The iris was fibrotic, with a layer of vascularized tissue on its surface. Over this, and on the posterior surface of the cornea, were many clumps of monocytes and leukocytes (keratitis punctata). The pigment epithelium showed cysts. The ciliary body was solid and cellular.

"Choroid: The choroid was fibrotic and contained round cells. In places the pigment epithelium was proliferating.

"Retina: The retina was entirely detached by albuminous exudate, in which were many bubble, or foam, cells. The retina was atrophic; there were areas of fatty degeneration, as well as deposits of cholesterol crystals, the latter surrounded by foeign body giant cells.

"Optic Nerve: The nerve was atrophic, as evidenced by irregular columns of nuclei.

"The diagnosis was glaucoma secondary to uveitis and retinitis, classifiable as Coats's disease."

It is well known that one form of Coats's all-inclusive disease is frank angiomatosis, and for that reason this case is presented as one in which a yellow reflex was caused not by retinoblastoma, but by the rarer angiomatosis.

In this resume are included three types of the common yellow pupillary reflex complexes; but detachment of the retina, which may at times be confusing, is not discussed, nor is the rare cysticercus in the vitreous considered.

A plea is made for a careful differential diagnosis in order to save the eye when possible and to remove a tumor as soon as the diagnosis is confirmed.

Because of the danger of transmitting retinoblastoma from one generation to another, it is a measure of conservation to advise against future pregnancy in a family in which more than one child has the disease.

I cannot at this time subscribe to the view that 1 case is sufficient to condemn the family to a childless existence.

Dr. John J. Clemmer made the pathologic reports except in case 6.

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PRACTICAL APPLICATION OF THE DENERVATED IRIS

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IT HAS LONG been known that the neuroeffector mechanism of denervated autonomic structures becomes sensitive to circulating hormones. This was stated by Cannon in 1939 as a law of denervation.[1]

> When in a series of efferent neurons a unit is destroyed, an increased irritability to chemical agents develops in the isolated structure or structures, the effect being maximal in the part directly denervated.

This phenomenon of sensitization had been observed as far back as 1855, when Budge[2] showed that the sympathetically denervated iris dilates in response to injections of epinephrine so small as to have no effect on the normal iris. Edes,[3] in 1869, corroborated these findings and also showed that the vessels in the denervated ear of the rabbit became intensely constricted when the animal was excited. At that time the reason for this phenomenon was not understood.

In 1904, Meltzer and Auer[4] studied the "paradoxic" pupillary dilation caused by epinephrine and the influence of this drug injected subcutaneously on the eyes of cats after removal of the superior cervical ganglion. Hartman, McCordock and Loder,[5] in 1923, showed that the iris deprived of its sympathetic supply became sensitive to pain, fear and cold and that this effect could be eliminated by bilateral adrenalec-

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tomy. In 1935, Hampel[6] studied the responses of the nictitating membrane of cats after denervation. He showed that the phenomenon of sensitization reached its height in eight days. He also demonstrated the important fact that the sensitization observed after postganglionic sympathectomy is about twice that observed after preganglionic sympathectomy.

These findings have not been without practical value. The phenomenon of sensitization which accompanies postganglionic sympathectomy is now well recognized. The observations of White, Okelberry and Whitelaw[7]; Hampel,[6] and Grant[8] adequately demonstrated that the response of denervated structures to circulating epinephrine and sympathin is more than twice as great after postganglionic as after preganglionic sympathectomy.

White and Smithwick,[9] in their excellent text on the autonomic nervous system, suggested that this phenomenon could explain the poor results of cervicothoracic ganglionectomy in cases of Raynaud's disease of the hand, in contrast with the good results obtained with lumbar ganglionectomy for vasospastic phenomena in the foot. In cases of the latter, after removal of the second and third lumbar ganglions, the postganglionic neurons to the sciatic nerve, which originate in the fourth lumbar and the first, second and third sacral ganglions are still intact. Thus, this operation is a preganglionic sympathectomy. Resection of the inferior cervical and first and second thoracic ganglions destroys most of the cells which give rise to postganglionic fibers to vessels of the arm. This operation is a postganglionic sympathectomy. This important and fundamental fact has been corroborated by many, including Lewis[10]; Simmons and Sheehan,[11] and Foerster.[12]

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Recently, it has been suggested that the denervated iris of the cat may be used as a sensitive indicator of the epinephrine level of the blood (Bender[13]). This investigator noted the minimal amounts of epinephrine required to cause minimal dilation of the sensitized pupil in cats anesthetized with ether and "pentobarbital."

It has been my experience that the denervated iris of the cat is too sensitive an indicator of the epinephrine content of test solutions. The mere act of injection in nonanesthetized animals causes an output of epinephrine which far exceeds the small amounts usually tested for. The attempt to anesthetize these animals causes enormous amounts of epinephrine to be produced (see experiment 1). Stimuli, such as the crack of a gun, a bark or a feint at striking, all cause dilation of a normal pupil. Thus, so much epinephrine is produced that a reaction is obtained not only in the denervated iris but also in the normal, nonsensitized pupil. Nevertheless, one can gain valuable information as to how long certain stimuli cause a heightened level of epinephrine in the blood to exist. For example, if a stimulus is adequate to cause dilation of a normal pupil (as well as the sensitized pupil, of course), one can get some idea of the epinephrine level produced by this stimulus if one observes the differences in dilation of the two pupils and, more important, the difference in time required for the pupils to return to their original sizes.

It is assumed, of course, that the indicator of a normal epinephrine level in the blood is not the return of the nonsensitized pupil to its normal size (after a stimulus), but, rather, the return of the sensitized pupil, as indicated by the fact that very small increases in the epinephrine level will produce dilation of the sensitized pupil and may yet be too small to cause the normal pupil to dilate.

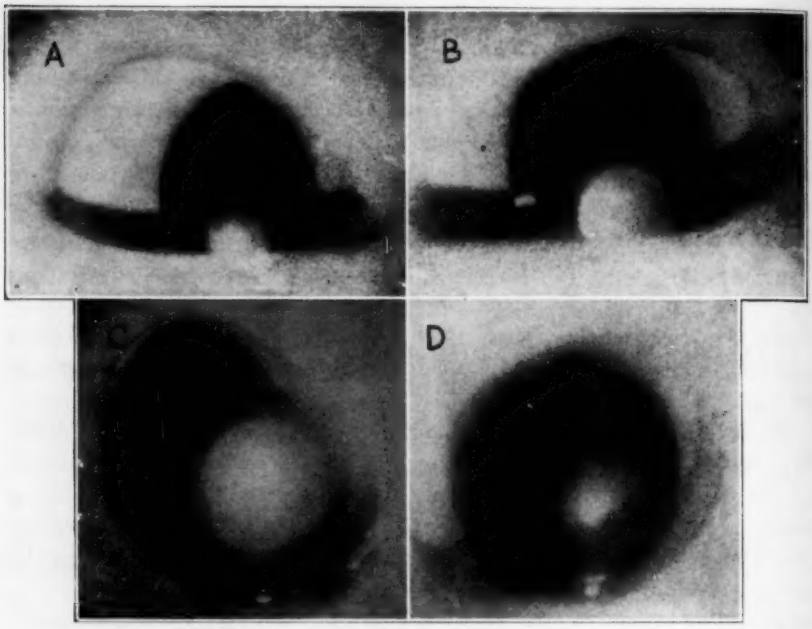
Practical application of these principles is demonstrated in the experiments which follow.

EXPERIMENTAL STUDY

EXPERIMENT 1.—Cats were chosen because of the high development of the sympathetic nervous system in these animals. Both male and female animals were used, the weights ranging from 4.8 to 7.2 pounds (2.4 to 3.6 Kg.). Postganglionic cervical sympathectomy was performed on the right side of each of 8 animals. The nerve section was performed 2 to 4 mm. superior to the superior cervical ganglion. None of the branches of the ganglion were cut. The nictiating membrane was removed bilaterally. Horner's syndrome was apparent within ten seconds after the sympathectomy in all animals, and the law of denervation was manifested before the tenth postoperative day, but in none of the animals did the phenomenon of

13. Bender, M.: Sensitized Pupillary Dilator and Facial Muscles as Indicators of Sympathetic and Parasympathetic Substances in the Blood, Proc. Soc. Exper. Biol. & Med. **39**:62, 1938.

sensitization appear before the second day. This observation is in agreement with the findings of other investigators. The sensitivity did not appear to be an "all or none" phenomenon. There were stages of sensitization, the height occurring on the fourth to the seventh day. This was manifested by a "paradoxic anisocoria." The pupil on the side of operation, which was small as a result of the sympathectomy (Horner' syndrome), was now larger than the normal pupil. The palpebral fissure on the side of operation became wider than its fellow. In all cats a prominent enophthalmos took place after operation. However, during the height of sensitization (four to seven days after operation) most of the cats (6) showed exophthalmos.



In taking the photographs of the pupil, infra-red illumination was used, since it does not alter the size of the pupils. Only the pupil is shown; the lids are not included. The round, white corneal reflexes of the infra-red lights are prominent. The horizontal black shadow at the lower margin of the pupil is the shadow cast on the eye of the lower lid.

A shows the denervated pupil at rest. It is small, owing to the Horner syndrome. *B* shows the normal pupil at rest, and *C*, enlargement of the denervated pupil with the animal under ether excitement. Exophthalmos is present, hence there is no shadow of the lower lid. *D* shows enlargement of the normal pupil under ether excitement.

These changes could be observed while the cat was at rest, and under no emotional stress, during this period. After the seventh postoperative day the picture reverted to the Horner syndrome seen immediately after the sympathectomy. Pupillographic changes were noted in these animals, and they will be the subject of another paper.

The present studies were made on these animals two to five months after operation. The animals still showed a Horner syndrome on the right side, with

no evidence of regeneration. They appeared at this time exactly as they did after the seventh postoperative day.

Each cat was placed in a cat box with the head protruding. Photographs were taken of the state of the pupils after fifteen minutes' rest in the box (figure, *A* and *B*). The animal was then subjected to ether anesthesia. The normal pupil dilated as the cat went into the stage of excitement, but the opposite pupil dilated maximally (figure, *C* and *D*). The Palpebral fissure widened, and exophthalmos

TABLE 1.—*Cats Subjected to Postganglionic Sympathectomy*

Cat No.	Duration of Ether Anesthesia, Min.	Time for Denervated Pupil to Become Normal, Min.
18	3	45
27	3	50
22	2½	62
26	2	71
24	3	61
25	2½	63
9	3	65
16	2	53
		Average 59

was present in all 8 cats. After about two to three minutes of excitement, the animal went into the first plane of surgical anesthesia (stage 3). The dilated normal pupil contracted. Anesthesia was discontinued. The sympathectomized pupil remained large. The time for this pupil to return to its preanesthetic size was noted, an average of fifty-nine minutes being required (table 1).

It has been stated that there is some sensitivity of structures after preganglionic sympathectomy. The sensitivity is about one-half that seen after postgang-

TABLE 2.—*Cats Subjected to Preganglionic Sympathectomy*

Cat No.	Duration of Ether Anesthesia, Min.	Time for Denervated Pupil to Become Normal, Min.
20	2	36
28	3	30
21	3	26
15	2½	28
29	2½	39
		Average 32

lionic sympathectomy. Therefore, to check the results described, 5 animals were selected for preganglionic section on the right side. The nerve was cut 1 to 2 cm. inferior to the superior cervical ganglion. Horner's syndrome was again apparent in less than ten seconds. The experimental work with ether was performed exactly as described for the animals undergoing postganglionic sympathectomy. The work was done two to four months after operation. The period of sensitization seen four to seven days after operation was never observed in these animals. However, ether

anesthesia was capable of causing excitement to the degree that the pupil on the side of operation became larger than the pupil on the normal side, but never as large as the pupil on the side of postganglionic sympathectomy. The time for the right pupil to return to its original size was noted. From the results in table 2, it is seen that this pupil takes less time to return to its preanesthetic state than the pupil with postganglionic sympathectomy. It required an average of thirty-two minutes for the former and fifty-nine minutes for the latter.

Comment.—It is generally known that the stage of excitement during ether anesthesia is accompanied with a great outpouring of epinephrine. In normal persons equal pupillary dilation occurs. During the first plane of stage 3 the pupil becomes smaller, accompanied with a drop in the level of epinephrine. The pupil becomes larger again as anesthesia deepens, but this is due to direct sphincter paralysis. It is thought that the level of epinephrine begins to approach normal while the patient is in the first plane of surgical anesthesia. However, does the epinephrine level become normal? The question then arises: Does ether itself cause production of epinephrine? I set out to prove that ether is sympathomimetic, i.e., that ether causes production of epinephrine not only in the stage of excitement of anesthesia but during the third stage, which follows.

With this in mind, the results are analyzed. In the first plane of stage 3, the epinephrine level is above normal, since the sensitized pupil is maximally dilated; but it is decreasing, since the normal pupil has contracted. After the discontinuance of anesthesia, an average of fifty-nine minutes was required for the sensitized pupil to return to its original size. It is repeated that this is the interval required for the epinephrine level of the blood to assume its normal value. Thus, the amount of epinephrine produced during the stage of excitement required fifty-nine minutes to be metabolized.

The work done with the cats subjected to preganglionic sympathectomy serves as a check on these observations. Since the sensitization in these animals is only about half that in the cats undergoing postganglionic sympathectomy, the difference between the pupils would not be expected to be as large, and the sensitized pupil would be expected to return to its normal size sooner than the pupil after postganglionic sympathectomy. In all cases this assumption was borne out. Consequently, normal size of the sensitized pupil with preganglionic sympathectomy does not indicate a normal epinephrine level, since this pupil is less sensitive than the pupil with postganglionic sympathectomy.

Even small increases of epinephrine for extremely short intervals can be detected. By utilizing the pupillographic method developed by O. Löwenstein, one can demonstrate by means of serial photographs of the pupil the length of time necessary for the dilated sensitized pupil to return to its usual size, even if it is only a fraction of a second. Stimuli such as

the crack of a gun, a laugh or a shout cause increased epinephrine levels in the blood. Needless to say, the denervated iris of the cat indicates not how much, but, rather, for how long the epinephrine level is increased. However, it is reasonable to assume that the length of time it is increased is a function of the height of the increase.

EXPERIMENT 2.—It will be shown that ether itself is sympathomimetic. It is not correct to assume that once a patient reaches the first plane of surgical anesthesia epinephrine is no longer being produced. However, the rate of production in stage 3 is much less than that in stage 2.

The animals in the first experiment were used. The same conditions prevailed. Each animal was given ether sufficient to carry it through the stage of excitement into the second plane of surgical anesthesia. At this point the normal pupil contracted, after having dilated during the stage of excitement. The sensitized pupil, which had dilated maximally in the stage of excitement, showed no change. The animals were then maintained in the second plane of stage 3. In each animal the sensitized pupil became slightly smaller than its size during the stage of excitement. However, it never approached its preanesthetic size, and in no cases did it become as small as the normal pupil, even after four to five hours of anesthesia.

Comment.—If no epinephrine had been produced after the stage of excitement, the experiment would have proceeded like the first one; i.e., the sensitized pupil would have returned to its preanesthetic size in about fifty-nine minutes in spite of the fact that the ether was still being given. This demonstrates that production of epinephrine proceeds as long as ether enters the blood stream. Thus, epinephrine is being produced continuously throughout any operation with ether anesthesia.

In 1912, Elliott[14] noted that ether caused a reduction in the epinephrine content of the adrenal glands. Bhatia and Burn,[15] in 1933, reported that ether caused a general stimulation of the sympathetic nervous system, manifested by the characteristic response of the organs innervated. The hypothalamus may be the seat of this stimulation. Barbiturates, which act on nuclei of the brain stem, are known to prevent this production of epinephrine. Barbiturates given intravenously or directly into the hypothalamus are effective in eliminating cardiac arrhythmias in chloroform anesthesia attributed to sensitivity to epinephrine (Dikshit[16]). It follows, then, that ether is a good anesthetic in cases of hyperinsulinism because of the production of epinephrine. However, "amytal" can prevent ether hyperglycemia (Banerji and Reid[17]).

14. Elliott, T. R.: The Control of Adrenalin Secretion, J. Physiol. **64**:274, 1912.

15. Bhatia, B. B., and Burn, J. H.: Action of Ether on the Sympathetic Nervous System, J. Physiol. **78**:257-270, 1933.

16. Dikshit, B. B.: Production of Cardiac Irregularities by Excitation of Hypothalamic Centers, J. Physiol. **81**:382-394, 1934.

17. Banerji, H., and Reid, C.: Adrenals and Anesthetic Hyperglycemia, J. Physiol. **78**:370-380, 1933.

The toxic effect of ether on the heart is relatively slight. Chloroform is twenty-five to thirty times as toxic. Although ventricular fibrillation is commonest during chloroform anesthesia, Guedel[18] pointed out that this must be considered a potential danger in every case of anesthesia, no matter what agent is used. He cited several cases which illustrate the relation of ether and epinephrine to ventricular fibrillation. Cyclopropane not uncommonly sensitizes the heart to epinephrine. Therefore, all possible measures to keep production of epinephrine at a minimum must be taken. Many anesthetists use small amounts of ether to eliminate arrhythmias during cyclopropane anesthesia. From what has been shown here regarding the sympathomimetic effect of ether, this constitutes a hazardous procedure.

EXPERIMENT 3.—A third experiment was finally performed. Three grains (0.19 Gm.) of "sodium amytal" was given intraperitoneally to each of the 8 animals with postganglionic sympathectomy. One hour later ether was administered to the animals. In no animal did the sensitized pupil remain dilated for more than ten minutes after the ether was discontinued, in the first plane of stage 3 (table 3).

TABLE 3.—*Relation of Barbiturates to Production of Epinephrine*

Cat	Time for Denervated Pupil to Become Normal, Min.*
18	7
27	5
22	10
26	8
24	9
25	7
9	10
16	9
	Average 8

*Readings were begun one hour after intraperitoneal injection of "sodium amytal."

Comment.—These observations prove that barbiturates will inhibit the production of epinephrine. Morphine will not prevent hyperactivity of the sympathetic nervous system. Consequently, since epinephrine is produced throughout the course of anesthesia, since ventricular fibrillation due to sensitivity to epinephrine may occur anywhere in anesthesia and since barbiturates are capable of inhibiting production of epinephrine, it is maintained that a barbiturate should be included as part of the medication before ether anesthesia.

18. Guedel, A.: Inhalation Anesthesia, New York, The Macmillan Company, 1944.

SUMMARY

Contributions to the development of the law of denervation are cited.

The denervated iris of the cat is too sensitive an indicator of the epinephrine content of foreign solutions, but may be used as a very sensitive indicator of the increase in the epinephrine level of the blood provoked by any stimulus exerted on that animal.

There may be an increase in the epinephrine content of the blood without dilation of the normal pupil. In fact, relatively large increases in the epinephrine level are required before the normal pupil begins to dilate.

The stage of excitement of ether anesthesia causes an output of the epinephrine; the amount produced required 8 cats an average of fifty-nine minutes to metabolize it.

Ether is sympathomimetic and causes production of epinephrine even after the stage of excitement (stage 2) of ether anesthesia.

Barbiturates are capable of inhibiting the production of epinephrine due to ether anesthesia, and their use is therefore recommended as valuable preanesthetic medication whenever ether anesthesia is used.

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CLINICAL ANISEIKONIA

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FOR THE PURPOSE of investigating the value of iseikonic glasses, a study was made of the 1,027 patients examined for aniseikonia at the Institute of Ophthalmology of the Presbyterian Hospital, New York, between December 1936 and December 1941.[1] These patients were referred for the examination by ophthalmologists and characteristically were those whose complaints bore a close relation to the use of the eyes and on whom the usual ocular therapeutic measures had been tried without relief being obtained. At the conclusion of the examination of the patient a report of the result was sent to the physician who had referred the patient. The trial of iseikonic glasses was not advised merely because aniseikonia was demonstrated, but the opinion was given that a factor was revealed by the examination which had not previously been corrected and which it was possible to correct. The decision whether iseikonic glasses were to be prescribed was left to the physician who had referred the patient for the examination.

Whenever possible, the refractive correction reported by the referring ophthalmologist was used as the basis of the test for aniseikonia. This was done to eliminate a change in the refractive correction influencing the result. In the small number of cases in which it was found necessary to make a change, it was usually possible to allow the patient to wear the correction both with and without the iseikonic factor in order that an accurate interpretation of the result could be made. This was accomplished by the almost routine use of trial or temporary lens sets, which consisted of the usual power lenses in the frame, the size, or aniseikonic, correction being added by fit-over lenses accurately adjusted over one or both eyes.

Miss Catherine Rittler gave technical assistance in this study.

Read at the Eighty-Third Annual Meeting of the American Ophthalmological Society, Hot Springs, Va., June 6, 1947.

From the Department of Ophthalmology, Columbia University, College of Physicians and Surgeons, and the Institute of Ophthalmology of the Presbyterian Hospital in the City of New York.

1. Ames, A.; Gliddon, G. H., and Ogle, K. N.: Size and Shape of Ocular Images: Methods of Determination and Physiologic Significances, Arch. Ophth. 7:576 (April) 1932.

The attempt was made to eliminate the effect of the extraocular muscle balance in the estimation of the results. In no case was a prismatic correction added to the iseikonic prescription when it had not been previously included in the correction worn by the patient. In no case was the strength of the prismatic correction already worn by the patient changed, except that in 11 instances small prismatic corrections were omitted in the iseikonic lenses prescribed for patients in the group showing improvement, when they were not considered a necessary component of the prescription and investigation had revealed that they were not a factor in the relief of the symptoms of which the patient complained.

It was recognized that the correctness of the patient's conclusion as to the relief of symptoms was difficult to estimate, and every effort was made to reach an accurate evaluation. This was done by direct report from the patient and from the physician who referred the patient for the examination. In some instances, while relief of symptoms was reported by the patient, the iseikonic lenses were not worn; in others, the correction was worn, even for years, in spite of the fact that no benefit was received. The influence of psychotherapy as the result of a rather formidable examination and the prescription of a radically new type of correcting lens was recognized. This, presumably, was the explanation of the cases in which relief from the symptoms of which the patient complained was obtained as soon as the iseikonic glasses were worn, but was followed by a gradual return of the symptoms in the course of a few weeks or months, during which time the correction continued to be worn.

A preliminary analysis of the results obtained was made on the basis of an interval of from three to six months after the prescription of the iseikonic glasses. Of the 1,027 patients examined, 527 showed demonstrable aniseikonia, and of these, there were 463 who received the correction for whom the result could be estimated. Of those receiving the glasses, 365 (79 per cent) were considered to have been relieved of all or a part of their symptoms, and 98 (21 per cent) were not benefited.

In 1946, from five to ten years after the original estimate was made, a questionnaire was sent to each of the 365 patients who were considered in the original analysis to have been benefited. Each patient was asked: "1. Are you still wearing the iseikonic glasses? 2. If you are no longer wearing them, how long did you continue to wear them? 3. Did you consider that you had been helped by them or not?" Replies were received from 206 of the original series of 365 patients. Of the patients who answered, 152 stated that they had been helped by the iseikonic glasses, and 54 said that they had not been benefited. In the preliminary analysis, 98 patients were classified as not benefited by the iseikonic

glasses, and 54 more were revealed by the questionnaire not to have been helped; thus, 152 of the original series were not benefited, and 152 reported improvement from use of the glasses. Therefore, of a total of 304 patients, after five to ten years, 50 per cent were benefited and 50 per cent were not benefited (table 1).

TABLE 1.—*Results of Wearing Aniseikonic Correction in a Series of 463 Patients*

Patients examined for aniseikonia (1936-1941)	1,027
Prescriptions given	527
Prescriptions filled	463

Results of Wearing Prescription	Three to Six Months		Five to Ten Years	
	No.	%	No.	%
Improvement	365	79	152	50
No improvement	98	21	152	50
	463		304	

TABLE 2.—*Symptoms in Series of Patients with Aniseikonia*

	Entire Series (463)		Three to Six Months				Five to Ten Years			
			Improvement (365)		No Improvement (98)		Improvement (152)		No Improvement (152)	
	No.	%	No.	%	No.	%	No.	%	No.	%
Fatigue, near vision	386	83	315	87	71	72	116	76	104	68
Headaches	307	66	238	65	69	70	92	61	103	68
Pain or discomfort	243	52	182	50	61	62	72	47	85	56
Fatigue, distance	236	51	186	51	50	51	73	48	69	45
Photophobia	216	47	172	47	44	45	55	36	64	42
Burning and itching	111	24	91	25	20	20	24	16	33	22
Panorama sickness	100	22	75	20	25	26	25	16	36	24
Blurring	86	19	68	19	18	18	16	11	25	16
Vertigo	69	15	48	13	21	21	15	10	31	20
Nausea	65	14	44	12	21	21	14	9	28	18
Lacrimation	42	9	30	8	12	12	6	4	16	11
Confusion	35	8	23	6	12	12	9	6	14	9
Pulling sensation	18	4	11	3	7	7	4	3	13	9
Slow reading	14	3	13	4	1	1	6	4	2	1

The records of the patients who had received aniseikonic corrections were studied to determine, if possible, what factors might suggest the presence of aniseikonia and, if present, whether its correction might result in benefit to the patient.

Analysis was made by sex, age and vocation of the cases in which the aniseikonic correction was tried. There were approximately as many male (46 per cent) as female subjects (54 per cent). The youngest patient examined was 5 years of age, and the oldest 70, with the fourth and

fifth decades having the largest numbers and with the third and sixth decades almost as well represented. The actual vocations were of no significance except that intense use of the eyes in the range for near vision, and less frequently in the range for distance, was common to all.[2]

In an endeavor to determine whether any symptom was of significance, a classification was made of the number of patients and the percentage of the group under consideration who complained of the symptom. There was a close correspondence in the incidence of the symptoms not only for the entire series but for both the groups showing improvement and the groups not showing improvement. The nature of the symptom of which the patient complained appeared to be of no significance in the estimation of the presence of aniseikonia. These symptoms were similar to those for which a patient seeks assistance from the ophthalmologist. The only significant factor was an association between use of the eyes and the difficulty of which the patient complained[3] (table 2).

TABLE 3.—*Refractive Errors of Patients with Aniseikonia*

	Entire Series (463)		Three to Six Months				Five to Ten Years			
			Improvement (365)		No Improvement (98)		Improvement (152)		No Improvement (152)	
	No.	%	No.	%	No.	%	No.	%	No.	%
Isometropia Emmetropia	10	2	10	3	0	0	6	4	2	1
Equal error	41	9	35	10	6	6	10	7	13	9
Anisometropia, opters										
0.12—0.25	156	34	126	34	30	31	65	43	48	32
0.37—1.00	164	35	120	33	44	45	42	28	61	40
1.12—2.50	60	13	49	13	11	11	19	11	20	13
2.62 and over	32	7	25	7	7	7	10	7	8	5

As anisometropia has been thought to contribute to the presence of aniseikonia, the records of the patients receiving aniseikonic corrections were studied in order to compare the refractive errors of the two eyes by estimating the maximum difference of the dioptric correction in whatever meridian this occurred as a basis of the classification of the anisometropia. In the entire series there were 51 patients (11 per cent) with isometropia, while 207 (45 per cent) had a difference of less than 0.37 D. in the refractive error of the two eyes. In only 32 patients (7 per cent) was there a difference greater than 2.50 D. The close correspondence of the incidence of anisometropia in the entire series and in the two

2. Berens, C., and Loutfallah, M.: Aniseikonia: Study of Eight Hundred and Thirty-Six Patients Examined with Ophthalmo-Eikonometer, Am. J. Ophth. **22**:625 (June) 1939.

3. Burian, H. M.: Clinical Significance of Aniseikonia, Arch. Ophth. **29**:116 (Jan.) 1943.

groups of patients with and without improvement from the aniseikonic correction suggested that the relation between anisometropia and aniseikonia[4] was not close (table 3).

The magnitude of the refractive errors did not seem to influence the results, as errors ranging from —9.50 to +13.50 D. were included in

TABLE 4.—*Distribution of Magnitude of Aniseikonic Correction in Patients Benefited and in Those Not Benefited by Correction*

Per Cent	Three to Six Months			Five to Ten Years		
	Improvement (365)			Improvement (152)		
	Over All	Meridional	Mixed	Over All	Meridional	Mixed
0.50—1.00	65	61	5	34	30	3
1.25—2.00	41	73	70	18	29	30
2.25—3.00	3	7	26	1	4	3
3.25—4.00	1	1	7	0	0	0
4.25—5.00	1	1	2	0	0	0
5.25 and over	1	0	0	0	0	0
	No Improvement (98)			No Improvement (152)		
0.50—1.00	17	26	2	27	34	4
1.25—2.00	8	15	19	14	28	29
2.25—3.00	0	2	5	0	2	8
3.25—4.00	0	1	2	0	1	4
4.25—5.00	0	0	0	0	0	0
5.25 and over	1	0	0	1	0	0

TABLE 5.—*Incidence of Magnitude of Aniseikonic Correction in Patients Who Were Benefited and in Patients Who Were Not Benefited by Iseikonic Correction*

Per Cent	Three to Six Months		Five to Ten Years	
	Improvement (365) Per Cent	No Improvement (98) Per Cent	Improvement (152) Per Cent	No Improvement (152) Per Cent
0.50—1.00	36	46	43	42
1.25—2.00	50	43	49	47
2.25—3.00	10	7	7	7
3.25 and over	4	4	1	4

the series and surprisingly satisfactory results were obtained in persons with insignificant or no refractive errors.[5] It was my impression that neither the magnitude of the refractive errors nor the anisometropia was significant in the relief of symptoms with the use of iseikonic glasses.

A study of the magnitude of the aniseikonic correction included in the prescriptions revealed that the great majority of errors, when over-all

4. Carleton, E. H., and Madigan, L. F.: Relationships Between Aniseikonia and Ametropia, from Statistical Study of Clinical Cases, Arch. Ophth. **18**:237 (Aug.) 1937.

5. Hughes, W. L.: Aniseikonia in Emmetropia, Am. J. Ophth. **20**:887 (Sept.) 1937.

or meridional, were between 0.50 and 2.00 per cent, and when a combination of the two types, were between 1.00 and 3.00 per cent (table 4). Comparison of the incidence of the magnitude of the aniseikonia in the patients who were benefited and in those who were not benefited did not reveal any significant differences (table 5). It has been my practice to prescribe as low as 0.5 per cent either as an over-all or as a meridional correction, and this small amount has been as important in giving relief as has the use of larger corrections. The finding of the theoretic size difference as indicated by the amount of the anisometropia has not been commonly observed.

The reports of the 206 patients who answered the questionnaire were studied with regard to the length of time the iseikonic glasses had been worn. Of the 152 who had been benefited by the correction, 3 had ceased to wear the glasses within five years, and the remaining 149 had been wearing the correction from five to ten years. Of the 54 who reported that they had not been aided by the iseikonic glasses, 23 discontinued wearing the glasses within one year, 10 within two years and 16 more within five years, while 4 persons finally discarded the glasses after wearing them from five to ten years (table 6).

TABLE 6.—*Relation of Length of Time Iseikonic Glasses Were Used to Improvement*

No. of Years	Improvement	No Improvement
1	0	23
2	2	10
3	1	5
4	0	8
5	53	3
6	44	1
7	22	2
8	7	1
9	19	0
10	4	1
Total	152	54

CONCLUSIONS

1. No symptoms are characteristic of aniseikonia, but symptoms associated with use of the eyes not relieved by the usual ophthalmic therapeutic measures may be due to it.

2. The presence of aniseikonia cannot be anticipated on the basis of anisometropia or the magnitude of the refractive error.

3. It is not possible to anticipate whether the correction of aniseikonia will aid the patient.

4. Iseikonic glasses should be used only for the relief of symptoms, and then only after the failure of the usual ocular therapeutic measures to give relief.

5. Although the number of patients aided by iseikonic glasses is small, these patients are entitled to all the assistance that can be given them.

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MEDICAL VERSUS SURGICAL TREATMENT OF GLAUCOMA

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Although many textbooks state that the treatment of glaucoma is surgical regardless of the stage in which it is encountered in actual practice, this is not true. I am in accord with most of my associates, who treat every patient with glaucoma medically until such time as control of intraocular pressure is no longer maintained at a limit at which visual acuity and the visual fields may be conserved.

ACUTE CONGESTIVE GLAUCOMA

It is agreed by all ophthalmologists who have extensive experience with glaucoma that the acute congestive type should be treated with tension-reducing drugs for at least twenty-four hours, combined with sedatives sufficient to reduce pain and induce sleep. If the commonly used tension-reducing drugs are not effective within twenty-four hours, a basal iridectomy should be performed. If, however, the repeated use of physostigmine salicylate, for instance, 1 drop of a 1 per cent solution every ten minutes for six doses, followed by instillation of pilocarpine nitrate (1 per cent) every hour, or of methacholine chloride (20 per cent) and neostigmine methylsulfate (5 per cent), 1 drop every ten minutes for six doses, followed by pilocarpine nitrate (1 per cent) every hour, is effectual in reducing the intraocular pressure to such an extent as to bring about the return of normal vision, surgical intervention may be deferred.

I have treated a number of patients with acute congestive glaucoma without surgical intervention, and they have had only one attack. At present I have under my care at least 6 patients who have had one episode of acute congestive glaucoma and for whom surgical treatment has not been necessary. They have been carried along with medical treatment over a period of years. The oldest of these, a woman of 65, lost one eye from glaucoma following operation by another surgeon

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Lecture delivered at a meeting of the Section of Ophthalmology, Philadelphia County Medical Society, March 6, 1947.

and refused to permit operation on the other eye. She has normal vision in the remaining eye and has had no attack of acute glaucoma in this eye.

A second patient, aged 50, who had an acute attack of glaucoma, was prepared for operation at the Wills Hospital. However, the tension and vision returned to normal while he was in the hospital, after three days of medical treatment, and he then refused to have the operation. Vision and intraocular tension are still normal, and the fields of vision have been only slightly disturbed, after a lapse of four years.

On the other hand, there are innumerable cases of acute glaucoma in which operation has been performed and the tension reduced, but the visual acuity has been reduced also. I have no record of a single case, either in private or in clinical practice, in which a surgical procedure for acute glaucoma has not in itself resulted in some loss of vision. True, surgical measures in cases of acute congestive glaucoma reduce tension and restore vision, sometimes from complete blindness to normal acuity. This return of normal vision, however, is only temporary, for the surgical procedure has produced an abnormal condition, hastening opacity of the lens. Nevertheless, surgery is the only means at one's command when medical treatment with tension-reducing drugs fails. I wish to stress that the use of tension-reducing drugs should be exhausted before surgical intervention is contemplated.

With the introduction of di-isopropyl fluorophosphate ("DFP") a new remedy has been added, which may defer operative measures.

There are many cases of acute congestive glaucoma in which the acute stage may be converted into a quiescent stage, a condition not to be confused with chronic simple glaucoma. In other words, the acute wet type of glaucoma is completely resolved. The eye becomes dormant and normal in function with the use of mild miotics and enters a normal phase, or interlude, in which there are no signs of glaucoma for many years. Of course, unusual excitement may disturb that interval of quiescence and bring about another acute attack. The patient, however, mindful of this possibility, can maintain his equanimity by anticipating an emotional upset and can use miotic drugs during the period of his emotional excitement. But once a patient has glaucoma, he always has glaucoma. At least he is always a patient; just as is the patient with hypertension and the patient with diabetes.

CHRONIC CONGESTIVE GLAUCOMA

While acute congestive glaucoma is the very wet, spongy type, chronic congestive glaucoma is spongy to a less degree. The latter is not so fulminating in onset or so dramatic in its appearance. Although in

rare cases the acute wet type may lapse into the chronic congestive type, the latter oftenest has a history all its own. Its onset may be characterized by headaches, periodic disturbance of vision, presence of halos around lights, redness of the eye, dilated pupils (one or both) and difficulty in reading. These symptoms are sufficient to attract the attention of the patient and the examining physician.

In the acute attack, the tension may vary from 40 to 90 mm. or above, whereas in the chronic congestive type the tension varies only in the lower range of 20 to 60 mm. (These figures are not actual but approximate and should be considered only as a guide.)

TABLE 1.—*Data on 5 Eyes with Chronic Congestive Glaucoma In Which Iridectomy Was Performed**

Case No.	Years Treated	Tension, Mm.	Gains in Vision
1	10	66 to 25	Hand movements - 3/60
2	½	60 to 23	Hand movements - 6/15
3	7	45 to 20	2/60 - 6/9
4	4	56 to 26	2/60 - 6/21
5	6	56† to 22‡	2/60† - 6/12‡

Interpretation: Congestive glaucoma does best under medical treatment, followed by surgical and then medical treatment.

*These 5 cases of chronic congestive glaucoma, and the 47 cases of chronic simple glaucoma listed in table 2, form a series of 52 cases of glaucoma on active file in my clinic at Wills Hospital; analysis was made by Dr. J. Eisenberg, clinic assistant.

†First values.

‡Last values.

Treatment of the chronic congestive type of glaucoma is medical, with use of tension-reducing drugs, such as pilocarpine, pilocarpine and physostigmine, physostigmine alone or di-isopropyl fluorophosphate. In cases of this type the medical treatment may be carried on over a much longer period than in cases of the acute wet type, because the increased tension is not so promptly damaging as in the former. Also, with the chronic congestive type there is ample time for compensation in that the eye may tolerate intraocular pressures ranging from 20 to 40 mm. without the eyesight necessarily being affected and without serious changes in the visual fields. Control of the intraocular tension in this category of cases does not mean a reduction to normal, which is believed to be 20 mm. of mercury, but consists in reduction to a degree which the eye in question will tolerate. In like manner, hypertensive patients may feel uncomfortable if their blood pressure is reduced to 120 mm., and diabetic patients may be uncomfortable if their blood sugar is reduced to an arbitrary normal.

One must revaluate one's ideas as to normal pressure in a normal eye and the pressure tolerated by a glaucomatous eye. It is an error to reduce the pressure of a pathologic eye to the normal for a normal eye; just as it is wrong to reduce the blood pressure of a hypertensive patient to the normal for a normal patient, or the blood sugar of a patient with chronic diabetes to the normal blood sugar for a normal person.

Many patients with chronic congestive glaucoma may be maintained under medical treatment for months and years. The congestive, or mildly wet, stage may be transferred to a dry, or intermittent, period, in which the halos are no longer seen, vision has improved, the headaches have disappeared and the visual fields have remained sufficiently large for the purpose of the individual patient.

By far the majority of my private patients with acute or chronic congestive glaucoma are women. In the younger age group, from 40 to 50 years, occur the larger number of cases of acute congestive glaucoma, and the younger portion of the old age group, from 50 to 60 years, contributes the greater number of cases of chronic congestive glaucoma.

Medical treatment consists in the use of pilocarpine nitrate (1 per cent) in a buffered solution three times a day, the instillations being gradually reduced to two a day, and then one a day, as the symptoms recede. Should there be an intermittent flare-up of the condition, I recommend pilocarpine nitrate (1 per cent) three times a day and 1 drop of physostigmine salicylate, 1 per cent (buffered), at bedtime. When the patient no longer complains of visual symptoms and is free from headaches, I reduce the strength of the solution of pilocarpine to 0.5, or even 0.25, per cent, to be used once, at bedtime.

There are times when patients discontinue medication for reason of illness or family difficulties which interfere with the convenient use of the drug, and I find that the lapse of months without miotics has done no great damage in cases of chronic congestive glaucoma during the quiet period, or, in other words, that period in which compensation of intraocular pressure finds a satisfactory level.

If the patient has repeated exacerbations of increased intraocular pressure with symptoms, despite medical treatment, operation should be performed.

CHOICE OF OPERATION

The choice of operation for chronic congestive glaucoma depends, in a measure, on the amount of vascular injection of the eye at the time of operation. A fiery red, spongy eye requires basal iridectomy. When the eye is only mildly injected, and there are no signs of atrophy of the iris, an iridencleisis should be performed.

In no circumstances do I advise an Elliot trephination on an acutely inflamed, or even a partially inflamed, eye. It must be kept in mind that every surgical procedure on an acutely or a moderately inflamed eye results in definite damage from the operation itself. I repeat this statement because of its importance.

However, if one decides to operate in a case of chronic congestive glaucoma during the quiet interlude because vision is being lost and the fields of vision are rapidly being cut down, I recommend the Eliot trephination. My greatest objection to this operation at any time, however,

is that it is difficult to perform, even in the hands of those who do a great deal of surgical work. To recommend it as a procedure for the casual ophthalmic surgeon is not fair either to the patient or to the surgeon. Operation for any kind of glaucoma should be such that it can be performed by any surgeon in any part of the world and be foolproof against accident by the patient or the surgeon.

After operation, medical treatment must be continued, and usually is by all ophthalmic surgeons, until the intraocular tension is low enough to insure maintenance of vision and the visual fields. In experience, one finds hypotonia in many eyes after the Elliot operation or after iridencleisis, particularly after the former. Hypotonia generally causes loss of vision and loss of function of the eye. Of course, miotics should not be used in cases of hypotonia. The only cure for this condition is nature's method of filling in the drainage area, which has been made too large and is filtering too freely. If a surgeon could only estimate, even with a fair amount of accuracy, whether his surgical procedure would result in too much drainage or in too little! It is known, however, that a basal iridectomy never results in hypotonia.

CHRONIC SIMPLE GLAUCOMA

Relation to Senility.—This condition is a type of glaucoma associated with old age and is primarily due to sclerosis of the blood vessels and fibrosis of the tissues of the eyeball. I classify it as the dry form of glaucoma, in which the vascular injection plays a minor part. It is the glaucoma of the older portion of the old age group, between the ages of 60 and 80, and may be rightfully called the glaucoma of old age. It should not be compared with the wet types of glaucoma, in which the blood vessels undergo dilation and there is an acute or a subacute accumulation of fluids of variable degree in the interior of the eyeball.

In a survey of 1,876 cases of glaucoma at the Wills Hospital during the period from 1926 to 1935, inclusive, I found that chronic simple glaucoma constituted 73 per cent of all the cases of primary glaucoma, acute congestive glaucoma 11 per cent and chronic congestive glaucoma 16 per cent.

The type of glaucoma encountered most frequently in the practice of any ophthalmologist is that commonly called chronic simple glaucoma. It is not necessarily the end result of acute congestive or chronic congestive glaucoma, although in a few cases the congestive type may enter this stage if the patient lives long enough and the surgeon has not operated too hastily. Oftenest, however, chronic simple glaucoma is an entity in itself. It is merely the result of a pathologic change in the walls of the blood vessels, particularly in the region of the ciliary body, but associated with sclerosis of all the blood vessels of the eye, both

the anterior and the posterior segment. There is also fibrosis of the canal of Schlemm and of the spaces of Fontana, and the fibrosis of senility involves all cellular elements in the eye. While the congestive, or wet, types of glaucoma have as their mark of identification too much blood, the chronic simple type is characterized by an insufficient quantity of blood by reason of senile changes in the form of fibrosis, preventing the normal interchange of fluids which takes place in young tissue.

TABLE 2.—*Data on 47 Cases of Chronic Simple Glaucoma at Wills Hospital*

Vision*		5 to 10 Yr. (18 Cases)		2 to 5 Yr. (14 Cases)		2 Mo. to 2 Yr. (15 Cases)	
First	Final	Medical	Surgical	Medical	Surgical	Medical	Surgical
G	G	8	5	6	2	8	2
G	P	0	0	1	0	0	1
G	B	0	2	0	1	0	0
P	G	0	0	0	1	0	1
P	P	1	2	0	1	1	0
P	B	0	0	0	2	0	1
B	B	0	0	0	0	0	1

Interpretation: Good vision in eyes with chronic simple glaucoma is best maintained by medical treatment. Medical treatment, followed by surgical and then medical treatment, gives less satisfactory results.

*G indicates vision of 20/100 or better; P, vision of 20/400 to 20/100 (partial blindness), and B, blindness, with vision of less than 20/400.

TABLE 3.—*Effect of Chronic Glaucoma on Vision of 47 Patients**

	Blindness in Both Eyes		Partial Blindness in Both Eyes		Good Vision in One or Both Eyes	
	Medical	Surgical	Medical	Surgical	Medical	Surgical
5 to 10 yr.	0	2	1	2	8	5
2 to 5 yr.	0	3	1	1	6	3
2 mo. to 2 yr.	0	2	1	1	8	3
Total	0	7	3	4	22	11

25 medical patients; 22 surgical (13 on whom Elliot operations were done elsewhere; 7 with blind eyes).

Interpretation: Total blindness occurs less frequently in medically treated eyes.

*Blindness means blindness or vision under 20/400; partial blindness, vision of 20/400 to 20/100, and good vision, 20/100 or better.

Treatment.—The treatment for chronic simple glaucoma, therefore, is the treatment for senility. One must treat it kindly, gently, being conscious of the fact that senility is not a reversible process. True, in any stage of chronic simple glaucoma there may be occasional flare-ups resembling the wet types, because intermingled with senile cells there are always some cells which have retained the vitality to carry on. Usually, chronic simple glaucoma occurs in persons who do not have the cellular structure or the blood vascular system which can be provoked into an acute flare-up by the vasomotor and psychic stimuli to which younger tissues are subject.

I prefer medical treatment in all cases of chronic simple glaucoma for the duration of the patient's life even if the vision is not normal, the visual fields are cut down and the tension is not normal as compared with that of a young adult. I discourage surgical treatment for the

reduction of these symptoms, for most old people do not have normal vision or normal fields of vision and can get along very well with vision of much less than 100 per cent. It is only when the surgeon feels that the aged should have an intraocular tension equal to a fictitious normal and believes that the intraocular tension in an old person must equal a fixed normal on an artifical instrument that unnecessary surgical procedures are performed—not for the patient's "rainbows" but for the surgeon's, and a pot of gold!

The treatment I prefer is the use of miotics, principally pilocarpine nitrate, either a 0.5 or a 1 per cent solution, once daily, preferably at night, for the purpose of keeping the tension sufficiently low (or high) to give the patient freedom from symptoms. One should treat the patient with the idea of giving him comfort, rather than seek some artificial normal gage with an instrument which has neither feeling nor judgment.

I find that 70 per cent of all patients with chronic simple glaucoma can be made comfortable from the standpoint of visual function and mental happiness with medical treatment. When the intraocular pressure produces symptoms, I increase the strength of the miotic drug, either pilocarpine or physostigmine, or both, to bring about a reduction of symptoms sufficient only for relief. When I find that miotics are failing and the patient is losing his vision, then, and then only, do I resort to surgical measures.

ALLERGY TO SURGERY

The surgical operation must be simple and the technic such that any surgeon may be able to perform it with ease, and with as little damage as possible to the patient's eye. It must be borne in mind always that glaumatous eyes of old people do not tolerate surgical procedures well. Despite statements by some surgeons that age in itself is not a contraindication to surgical intervention, it is my personal experience that extensive, meddlesome and fancy operations should not be performed on old persons with chronic simple glaucoma. The mental trauma resulting from any kind of operation on an old person is sufficient to undermine his morale and his physical resistance so as to interfere with healing. I have known old people who faded away physically under my care at the Wills Hospital merely because they had undergone a surgical ordeal. I therefore emphasize that surgical treatment of chronic simple glaucoma, especially in very old people, should be considered only as a last resort, and then only if the surgeon can give some degree of assurance that his surgical skill will benefit the patient. It is easy to try something on some one else's eye. A rough, trial and error surgical procedure should not be inflicted on any one, especially the aged. I have seen blindness resulting from surgical treatment, or at least provoked by it, in too many eyes

with chronic simple glaucoma.

When one has no alternative but to operate, the operation of choice for chronic simple glaucoma is iridencleisis. The second choice is my modification of the Herbert operation, in which a trapdoor is made in the region of the pars plana of the ciliary body. Such a trapdoor does little or no damage to the already diseased eye, and it enables the accumulated fluids to reach the outside slowly and continuously. The third operation, and the least desirable, is the Elliot trephination. I personally have seen too many tragedies resulting from the Elliot trephination in the hands of skilled and of unskilled surgeons. It is an operation which cannot be performed with skill by the average ophthalmologist. I prefer an iridecleisis or the Herbert operation.

There are other types of operations mentioned in the textbooks, and other types of medical treatment to which I have made no reference, but I omit them because in my experience I have found they have of little or no value.

Before operating in any case of chronic simple glaucoma the ophthalmologist should remember that old people prefer a little sight with glaucoma to a blind eye that apparently has been cured of glaucoma.

MEDICAL VERSUS SURGICAL TREATMENT

Bothman[1] stated:

> Treatment of glaucoma is of two types, medical and surgical. Indications for surgery differ with the ophthalmologist. Some prefer to operate early, whereas others prefer to give miotics a fair trial first. The advocates of early operation put forth such arguments as (1) patients cannot be trusted to carry out treatment faithfully, (2) the patient may live a long distance from help in case of an acute attack, and (3) surgery eliminates use of drops (miotics). To some extent, they are correct, but every ophthalmologist has seen cases in which he later wished that surgery had been postponed. Complications and surgical accidents cannot always be avoided. With ignorant and uncooperative patients, medical treatment may be hazardous. However, we have seen a great many patients who faithfully carry out treatment for indefinite periods, 20 years or more.
>
> Acute glaucomatous attacks do not require emergency operations; in fact, such an operation may be disastrous. Every effort must be made to reduce the tension to normal or to as low a level as possible before surgery is attempted. It is hardly conceivable that in the United States a patient with an acute attack could not get help within four to six hours [page 7].
>
> The frequency with which trephine openings close or other types of operation fail to keep the tension within safe limits is familiar to everyone. Too large a percentage of patients require miotics postoperatively for one to be able truthfully to tell a patient that he will not need drops after surgery. The best that can be said is that he may not need them [page 8].

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1. Bothman, L., and others: 1945 Year Book of Eye, Ear, Nose and Throat, Chicago, The Year Book Publishers, Inc., 1946, pp. 7 and 8.

Duke-Elder stated:

To give a prognosis of a composite entity such as primary glaucoma is impossible. On the whole, however, it may be said that, although exceptions do occur, without treatment the disease is progressive and results in absolute bilateral blindness. With adequate treatment the majority of simple compensated glaucomas can be stabilized or their progress delayed so that useful vision remains until the death of the patient: fortunately most patients are old, but a juvenile glaucoma is an unpleasant problem. Quite a number, however, particularly those of the sclerotic type, gradually and imperceptibly go down-hill even although the tension is adequately controlled: the deterioration is part, although it may be the most conspicuous part, of a general pathological process which is beyond medical control. Again in this, as in all other types of glaucoma, a malignant form occurs, which progresses, and frequently progresses rapidly, despite all treatment. . . . In general terms it may be said in simple glaucoma that with reasonably adequate treatment some 70% of cases do well in so far as they become stabilized, 20% deteriorate so slowly that they retain a useful amount of sight to the end, while 10% do badly. In acute congestive glaucoma approximately the same figures can be obtained if the attack is overcome rapidly by medical treatment and a prophylactic operation is done on a quiet eye; but if the condition has lasted longer than 48 hours or if resort has been necessarily made to surgery of a more desperate type, the figures are considerably worse and a disappointing end-result in 30% is to be expected. In chronic congestive glaucoma, allowing for the great clinical variations be-'tween different cases, the figures lie between the former two [page 3414].

The local treatment to the eye is best considered separately for each clinical picture. It is to be remembered that *in every unilateral case the other eye should be held suspect* and every operation on one eye should be preceded by eserine in the other to eliminate the effect of axon reflexes between the two.

This last point is a matter of great importance. Any intra-ocular operation—apart altogether from glaucoma—is accompanied by a reflex hypo- or hypertensive reaction in the other (Towbin, Protopopow and Urishewaskaja,[3] 1934), and in an eye predisposed to glaucoma (as the fellow eye of a glaucomatous one frequently is even although it appears normal) this reflex reaction may be, and frequently has been, disastrous [page 3408].

Wills Hospital.

2. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1941, vol. 3, pp. 3408 and 3414.

3. Towbin, B. G.: Protopopow, B. W., and Urnishewskaja, W. S.: Ueber die Wirkung des operativen Eingriffes in eines der beiden Augen auf den intraokularen Druck des anderen Auges, Arch. f. Ophth. **131**:554, 1934.

RETROLENTAL FIBROPLASIA

A Preliminary Report

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OPACIFICATION immediately behind the lens appearing in infants at or within a short time of birth, often associated with persistence of the hyaloid artery and its branches, or other abnormalities of the vitreous and the inner layer of the secondary optic vesicle, has long been described in the literature. The difference between these abnormalities and glioma, or malignant fungus, and congenital cataract was recognized by early writers in ophthalmology. Travers,[1] in 1820, described the case of a child of 8 months in which he extirpated the globe and observed the vitreous filled with an "opaque lardaceous substance, by which the lens was slightly protruded and the iris rendered convex. The retina for the most part was absorbed, and the other tunics perfect." He also observed a child from the age of 3 months who had a similar condition, while the pupil of the other eye was constricted and closed by an opaque capsule. Frick,[2] in 1826, described what was apparently this condition as congenital cataract, appearing several days or weeks after birth. Wecker,[3] in 1866, observed a case of persistent hyaloid artery coexisting with a luxated cataract and cited Meissner, in 1857, and Saemisch and Zehender, in 1863, as describing persistent hyaloid arteries in man. Nettleship,[4] in 1873; Gardiner,[5] in 1880; Holmes,[6] in 1881; Vassaux,[7] in

Presented at the Alumni Meeting, Institute of Ophthalmology, of the Presbyterian Hospital, New York, May 1, 1948.

1. Travers, B.: Diseases of the Eye, London, Longman, Hurst, Reese, Orme and Brown, 1820, p. 203.

2. Frick, G.: Diseases of the Eye, London, John Anderson, 1826, p. 164.

3. Wecker, L.: Maladies des yeux, Paris, A. Delahaye, 1866, vol. 2, p. 300.

4. Nettleship, E.: Curator's Report 187: Vascular Cord Traversing Vitreous and Co-Existing with Great Plastic Inflammation of Hyaloid, Ophth. Hosp. Rep. London **7**:632, 1781-1873.

5. Gardiner, E. J.: A Case of Persistent Hyaloid Canal and Artery, Arch. Ophth. **9**:473, 1880.

6. Holmes, E. L.: A Case of Persistent Hyaloid Canal, Arch. Ophth. **10**:168, 1881.

7. Vassaux, G.: Persistance de l'artère hyaloïdienne et de la membrane pupillaire, ayant détermine des altérations intra-ocularies, simulant clinquement un néoplasme, Arch. d'opht. **3**:502, 1883.

1883, and numerous others later described this, or a similar, condition. Terry,[8] however, first called attention to the frequency of the condition in prematurely born infants and expressed the belief that the condition was different from that occurring in full-term infants. Reese and Payne[9] stated the belief that the same lesion may occur in both premature and full-term babies. Krause[10] described a large number of cases, in some of which the condition was associated with other defects of the central nervous system, particularly encephalic dysplasia. Cordes[11] has summed up the papers by these recent authors.

In studying the literature on this abnormality, and my own cases, comprising over 30, I came to the belief that the vascular fibrous tissue behind the lens was due to abnormal formation of the secondary and tertiary vitreous, causing an arrest of regression of the embryonic hyaloid vascular system, or at least a re-formation of this system, with revascularization of the abnormally dense vitreous structure. I concluded, also, that in certain instances there was vascularization of the already formed membrane from the peripheral retina, as evidenced by vessels radiating from the periphery to the center in the retrolental membrane, instead of from the center, as they usually did.

However, in observing the eyes of premature infants from birth, I rarely saw remnants of the hyaloid artery, and these disappeared shortly. None of these infants was born with a retrolental membrane. In 2 infants that I saw shortly after birth, nearly a year ago, without evidence of ocular abnormality, retrolental fibroplasia has since developed. I have therefore come to the conclusion that retrolental fibroplasia as it is usually known is not congenital, and is probably not related to uterine circumstances, except that of premature birth itself. The Owenses[12] have also recently stated that retrolental fibroplasia is not derived from the hyaloid vascular system but is preceded by dilatation of the retinal vessels, especially the veins, appearing first at about the age of 85 days, followed by peripheral detachment of the retina, with formation of the retrolental membrane, which appears at approximately the age of 100 days. They

8. Terry, T. L.: Extreme Prematurity and Fibroplastic Overgrowth of Persistent Vascular Sheath Behind Each Crystalline Lens, Am. J. Ophth. **25**:203, 1942.

9. Reese, A. B., and Payne, F.: Persistence and Hyperplasia of the Primary Vitreous, Tr. Am. Ophth. Soc. **43**:163, 1945.

10. Krause, A. C.: Congenital Encephalo-Ophthalmic Dysplasia, Arch. Ophth. **36**:387 (Oct.) 1946.

11. Cordes, F. C.: Types of Congenital Cataract, Am. J. Ophth. **30**:397, 1947.

12. Owens, W. C., and Owens, E. U.: Retrolental Fibroplasia, read at the seventh clinical meeting of the Wilmer Residents' Association, Baltimore, April 14, 1948.

saw the membrane develop in 15 cases. In some of these cases there were yellowish retinal exudates, but no retinal hemorrhages.

In only 1 case have I seen what appeared to be so-called retrolental fibroplasia begin and watched its development to completion. In this case, that of an infant weighing 2 pounds 10 ounces (1,191 Gm.) at birth, the retinal vessels began to increase greatly in caliber and tortuosity in the fifth week of life. Numerous striate, superficial, roughly oval retinal hemorrhages appeared also at this time. Arteriovenous communications formed between the retinal artery and its accompanying vein in some places, usually at the midperiphery, and sometimes the hemorrhage surrounded the junction of vein and artery. Most of the hemorrhages, some of the arteriovenous communications and the tortuosity disappeared in a week or two. However, when the arteriovenous communication remained, the portion of the vessels comprising the U remained large, but the distal portion of the retinal vessels shrank. In the eighth week a pink haze developed just anterior to an arteriovenous junction in the lower portion of the fundus of each eye, which was due presumably to extravasated blood from the dilated, thin-walled vascular loop. These areas increased in size and projected forward into the vitreous. In the tenth week blood vessels could be seen in the nebulous preretinal masses. As the nebulae increased in size, they became more vascularized and migrated centrally, obscuring the central portion of the vessels of their origin and then the disk, and gradually occupying the area of Cloquet's canal. Slowly the nebulae changed in character, becoming completely vascularized, denser, quite clearly defined and smaller in diameter, to become centrally placed, irregular columns extending forward from the region of the disk toward the lens by the growth anteriorly of vascular loops. These loops projected forward like fimbria from various places in the mass, with practically no supporting tissue. However, at the time of writing, in the fourteenth week of life, the deeper portions of the mass are changing color, from dark gray to dense white. The mass has reached the lens in each eye, but there may be some regression, due perhaps to the repeated transfusions. A large preretinal hemorrhage surrounding the base, and possibly arising from the angioplastic column, has been present in the left eye since the tenth week of life. The rest of the vitreous, which became quite hazy with the appearance of the preretinal nebulae, cleared for a time, and small retinal vessels running to the periphery could be seen. However, the vascular tissue in the right eye has spread from just temporal of center over the whole posterior surface of the lens, while that in the left eye has not changed.

In twins, weighing 3 pounds 10 ounces (1,644 Cm.) and 3 pounds 9 ounces (1,716 Gm.), respectively, who continued to have prominent pupillary membrane loops, the retinal vessels became tortuous, with racemose aneurysms, in the fifth week also, and at the same time the pupillary vessels became engorged. In these infants, as well as in all others at the beginning of the appearance of abnormal processes, the pupils dilated poorly with cycloplegics and mydriatics. This phenomenon lasted two or three weeks, or longer. In 1 of the twins, however, retinal hemorrhages appeared in only one eye. The infants were discharged during their sixth week of life and were not seen again for a month. When again examined, they had the angiofibrous columns in the vitreous extending from the region of the disk, similar to those in the first case, and in all four eyes the mass touched the lens. In the left eye of 1 of the twins the angioplastic mass is loosely knit and spread out, so that the optic disk and the origin of the vitreous vessels can be seen well because of the lack of intervascular tissue. All the main vessels of the vitreous have the appearance of being pulled forward into the vitreal

mass in front of the disk practically from their origin, and send only small branches onto the surface of the retina. Apparently, all the retinal portions of these retinal vessels have shrunk, owing to the parasitic vitreous branches. A preretinal hemorrhage surrounds the column in the vitreous of the right eye of the other twin. The pupillary loops, although present, have become very small in these eyes.

It appears that this formation of vessels in the vitreous might be the hyaloid vascular system when it is quite fully formed. However, in the first case, at least, the mechanism of its formation was seen to be leakage of blood from the retinal vessels into the vitreous, followed by vascularization of the hemorrhage in the vitreous from the retinal vessels. The hyaloid artery, or its remnants, were not persistent in any of these cases, at least by the second week after birth, and certainly played no part in the formation of the angioplasia of the vitreous. I feel sure that this condition, in time at least, if untreated, will became a typical retrolental fibroplasia by spreading over the posterior surface of the lens and opacifying the mass by the further formation of intervascular fibrous tissue. This formation seems to be akin to the formation of granulation tissue elsewhere in the body, to retinitis proliferans or to the syndrome of von Hippel's angiomatosis.

In these 3 cases, as well as in many others, the peripheral portion of the fundus was pale gray from birth, the pallor persisting for several weeks at least. In certain cases this appears to be due to peripheral detachment or to failure of coaptation of the peripheral retina, for the retina is opaque, flat and elevated, with retinal vessels running over it. However, in some cases this peripheral pallor seems to be due, at least in part, to a peripheral haze in the vitreous or to failure of the vitreous to clear peripherally, which may be the effect of a structural abnormality of the secondary vitreous there. The retinal vessels, when dilated in the 3 cases described, were dilated as far peripherally as could be followed, but they are, of course, attenuated now; the peripheral retina, however, is still pale, and perhaps elevated.

In another infant, weighing 2 pounds 4 ounces (1,020 Gm.) at birth, the retinal vessels remained consistently small, but the peripheral vitreous is still very hazy and the peripheral retina elevated, although it cannot be seen well. In the sixth week of life many small, striate retinal hemorrhages appeared, but disappeared by the next week. At the time of this report, in the tenth week, in certain portions of the fundus the central edge of a thin membrane can be seen lying close behind the periphery of the lens, and in the frontal plane of the eye. It is not vascular and appears to be due to a condensation of the peripheral portion of the vitreous. In 1 eye there is also a dark brownish red, sheetlike mass without visible vessels, of triangular shape, one point of which is in the midvitreous, not far back of the lens. Another point joins the peripheral membrane, and the third point attaches at the disk and is in contact with the retina for at least a portion of the way to the periphery, where it is lined with pigment along the sides, like a typical retinal fold. The vitreous has been so hazy during the development of the tissue last described that I cannot tell how it originated, but early in life the disk and the posterior portion of the fundus were clearly seen.

Blackfan and his associates[13] stated that in the premature infant during the first three months of life there are a rapid decrease in the number of red blood cells, and an even more rapid diminution in hemoglobin. This change is thought to be due to the same mechanism as that which influences the development of physiologic anemia in full-term infants. The premature infant grows at a relatively faster rate than the full-term infant; consequently, there are a greater demand for blood and a less actively functioning hemopoietic system. The anemia is characteristic of all premature children. The severity is proportional to the state of prematurity. In premature infants weighing 5 pounds (2,268 Gm.) or more at birth, the number of red blood cells and the hemoglobin concentration are not altered as much as in those weighing less. Severe anemia begins in the second week and continues to become severer until the eleventh or twelfth week, when the erythrocytes begin to increase steadily in number, until by the seventh month the values are those for full-term children of the same age.

There have been very low hemoglobin values and red blood cell counts in all the cases described, but we did not begin to make the blood studies early or frequently enough to permit the establishment as yet of a definite correlation between the pathologic process described and the anemia. There may be a correlation between transfusion of citrated blood and arrest, and perhaps regression, of the pathologic process in some cases, especially notable in shrinking of the new-formed vitreous vessels, retraction of the vitreous membranes and clearing of the peripheral vitreous.

Although at present unproved, it appears that the anemia of prematurity in itself may be a factor at least in the causation of retrolental fibroplasia. I do not mean that low hemoglobin and red blood cells alone are necessarily of significance; rather, a low or high concentration of some other, as yet unknown, substance in the blood may have a part in the anemia. The secondary vitreous, because of this anemia, may change in character or fail to develop normally, or may contain some substance which is irritating to the retinal vessels and stimulates formation of new vessels from the retina. At any rate, except for undoubted cases of embryonic arrest, I feel that it can be stated that so-called retrolental fibroplasia in premature infants is not congenital and is not due to persistence of the embryonic vascular structure, but that it is a postnatal pathologic condition in which the retinal vessels play a prominent role, but which appears to be stimulated by some abnormality of the vitreous.

This concept of the formation of retrolental fibroplasia, with secondary contractures and changes, would explain the pathologic picture in

13. Blackfan, K. D.; Diamond, L. K., and Leister, C. M.: Atlas of the Blood in Children, New York, The Commonwealth Fund, 1944.

the cases of the fully developed abnormality I have observed, as well as those described in the literature. There appear to be two main types of the condition. The first develops from the proliferation of vascular tissue from the retinal vessels of the posterior portion of the fundus into abnormal vitreous, probably usually with hemorrhage. The second is the result of failure of development or condensation of the secondary vitreous at the anterior periphery, with proliferation into it of retinal vessels from the unattached peripheral portion of the retina. There may be combinations of the two types. A similar intracranial pathologic process might well explain Krause's "encephalo-ophthalmic dysplasia." The occurrence of dilated retinal and pupillary vessels, the difficulty in dilating the pupils, the frequent finding of posterior synechias later, the anterior peripheral and prepapillary haze in the vitreous and the failure of normal enlargement of the globes in some cases seem to point to postnatal iridocyclitis and hyalitis as the basic pathologic process. The etiologic factor is at present obscure, but may well be a physicochemical pathologic process, affecting principally the ciliary body at a crucial period of development and the secretion of secondary and tertiary vitreous.

This paper is not a full report of the study, which will be completed later; rather, it is intended merely to be provocative of investigation by other workers, in the hope that this devastating process in infants may be prevented.

179 Allyn Street.

Clinical Notes

A SIMPLE APPOSITIONAL SUTURE FOR USE IN OPERATIONS FOR CATARACT

CHARLES A. PERERA, M.D.
NEW YORK

The effect of corneoscleral sutures in reducing the complications following operations for cataract has been demonstrated by many competent ophthalmic surgeons. These sutures may be classified into four main types: (1) sutures placed before the eyeball has been opened; (2) sutures anchored before the globe has been incised, and completed after the incision; (3) sutures placed after a keratome incision or after a short incision made with the Graefe knife, before the opening has been enlarged, and (4) sutures placed after the incision has been completed.

The ideal corneoscleral sutures are those which exactly approximate the wound edges, i.e., appositional sutures. Appositional sutures placed before the operative incision into the eyeball have been described by Verhoeff[1] and by McLean.[2] The latter author, after reviewing the literature, reported a modification of the suture originally described by Suarez de Mendoza in 1892 and reintroduced with variations by Lindner in 1938.

The trauma of inserting corneoscleral sutures may add to the risk of operation for cataract, especially in an eye containing a subluxated lens or a fragile zonular membrane. This trauma is negligible if the sutures are placed before the globe is opened, and minimal if the sutures are inserted when the incision into the anterior chamber is small and incapable of gaping.

There is an increasing tendency among ophthalmologists to make use of the keratome in performing operations for cataract, and then to enlarge the wound with scissors. Appositional sutures can be easily introduced after a keratome incision, as described here.

Read at the Eigthy-Fourth Annual Meeting of the American Ophthalmological Society, Hot Springs, Va., May 17, 1948.

From the Department of Ophthalmology, Columbia University College of Physicians and Surgeons, and the Institute of Ophthalmology of Presbyterian Hospital.

1. Verhoeff, F. H.: A Corneo-Sclero-Conjunctival Suture in Operations for Cataract, Tr. Am. Ophth. Soc. **25**:48-53, 1927.

2. McLean, J. M.: A New Corneoscleral Suture, Arch. Ophth. **23**:554-559 (March) 1940.

TECHNIC OF PLACING APPOSITIONAL SUTURES AFTER KERATOME INCISION

After the usual preoperative preparation of the patient, including akinesia, retrobulbar injection of procaine and placement of a traction suture through the superior rectus muscle, the lids are held apart by a

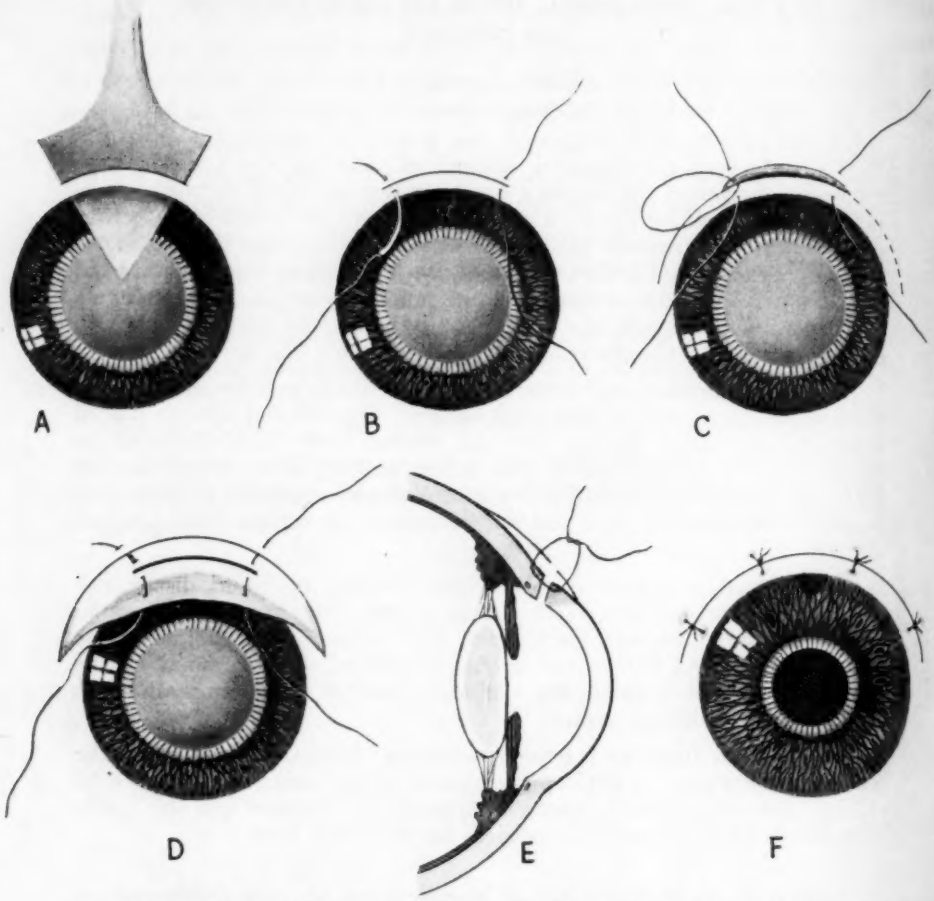

Fig. 1.—*A, B* and *C,* appositional sutures placed after keratome incision. The conjunctiva is not shown. *A,* limbal keratome incision; *B,* sutures passed through extremities of wound; *C,* suture looped out and incision completed.

D, E and *F,* appositional sutures with narrow conjunctival flap. *D,* sutures placed after 2 mm. conjunctival flap has been turned down over cornea; *E,* cross section of eyeball, showing one suture; *F,* appearance after completion of operation. The conjunctiva is closed with two additional sutures.

speculum, special clamps or lid sutures. A limbal keratome incision is made superiorly with or, if this is contraindicated, without a conjunctival flap. The limbal incision may be made with a Graefe or a Wheeler knife, and it may be placed in any quadrant desired. At this point, a

fine silk suture is passed through the anterior margins of the corneoscleral wound close to each extremity of the keratome or knife incision. If a conjunctival flap has been fashioned, the sutures are also passed through the conjunctival margins or in mattress style through the flap. These sutures are placed so close to the extremities of the wound that they bite into apposed portions of the wound edges. Fixation for this maneuver is obtained by applying scleral fixation forceps posterior to

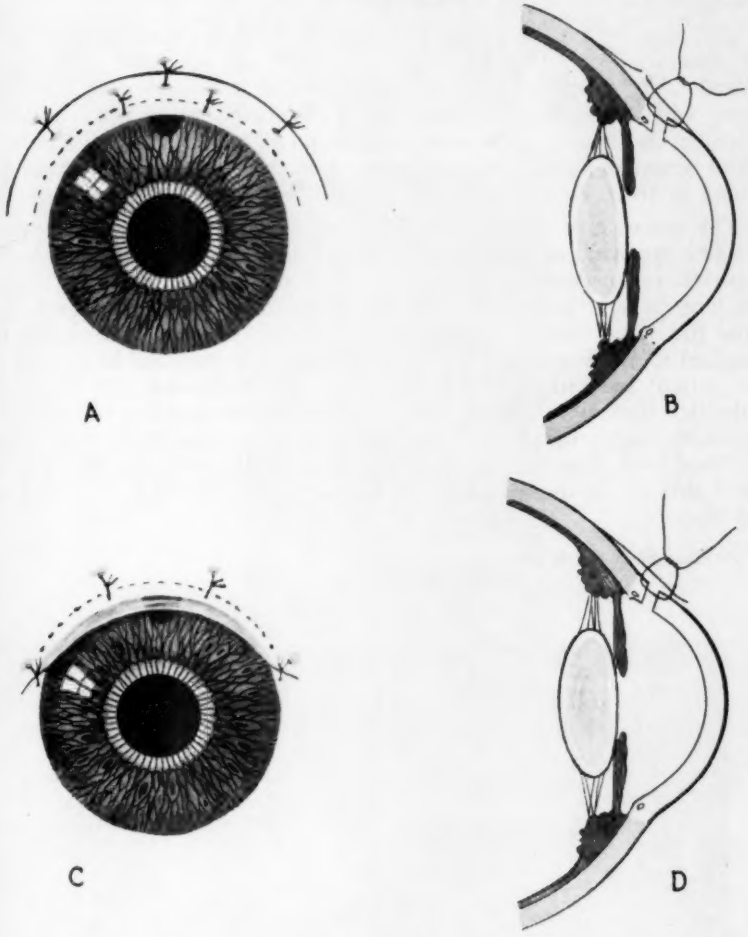

Fig. 2.—*A* and *B*, appositional sutures with large conjunctival flap. *A*, appearance at close of operation, showing corneoscleral sutures tied in mattress fashion through conjunctival flap. Conjunctival margins are approximated with three additional sutures. *B*, cross section through a corneoscleral suture.

C and *D*, appositional sutures with sliding conjunctival flap. *C*, appearance at completion of operation, showing corneoscleral sutures tied through conjunctival flap. Two laterally placed conjunctivoepiscleral sutures hold conjunctival flap in place. *D*, cross section through a corneoscleral suture.

the site of the suture, or by grasping a margin or the extremity of the wound with fine conjunctival forceps. Then the sutures are looped out of the incision, which is completed with scissors. At the close of the operation, additional sutures may be inserted into the conjunctival flap if indicated.

I have used these sutures for over ten years, with satisfactory results. This method of suturing has been employed by some of the resident ophthalmologists on the service of Dr. A. B. Reese at the Institute of Ophthalmology of Presbyterian Hospital.

One case of postoperative prolapse of the iris occurred in the last 100 cataract operations in which I made use of these appositional sutures. This series include 80 intracapsular extractions of the lens, among which were 6 loop extractions of dislocated lenses and 9 instances in which the lens capsule was opened accidentally or intentionally to permit grasp of a taut lens capsule. A complete iridectomy was performed in 46 cases, in 5 of these before the the cataract operation.

The instance of prolapse of the iris occurred in a man 81 years of age. The appositional sutures were placed as shown in figure 2*A* and *B*. A peripheral iridectomy was performed at the 12 o'clock position. The lens capsule tore at the site of application of the Arruga forceps below the lower border of the pupillary area, but the instrument was reapplied to encompass the tear and the lens was removed in its capsule. The patient got out of bed during the night following the operation. At the first dressing, three days after operation, the anterior chamber was filled with blood, which extended beneath the conjunctival flap. When the blood was absorbed, a small prolapse of the iris was seen on the lateral side of the temporal corneoscleral suture, beneath the conjunctival flap.

70 East Sixty-Sixth Street.

FIXATION LIGHT

JOHN V. McMACKIN, M.D.
MIAMI, FLA.

The screen test is being used oftener in examination of ocular motility than formerly. As a result, more apparatus is being devised for the technic. Some time ago I devised what I believe is the simplest, although perhaps not the most accurate, device to use in certain cases in which more elaborate apparatus cannot be used, especially in handling children and when one has no assistant or nurse to hold a target. The child now helps in the game to be played.

The apparatus consists of a metal wire fly swatter, with the swatter part sawed off; a National bulb holder and bulb attached to the end with adhesive tape, and cord running to the volt controller. This gives a handle 18 inches (45 cm.) long, with the bulb on the upper end.

With the patient seated in an ordinary arm chair, all the cardinal positions of gaze can be measured, the examiner watching only the central portion of the head, which he is watching anyway. After a little practice the examiner can have the light target in any position desired, with extreme comfort to the patient and plenty of space for the physician to make the screen test.

When the lower fields are to be examined, the patient holds the bulb holder at the arm of the chair.

406 Huntington Building (32).

Abstracts From Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

Anatomy and Embryology

THE TROCHLEAR NERVE IN THE HUMAN EMBRYO AND FOETUS. E. R. A. COOPER, Brit. J. Ophth. **31**:257 (May) 1947.

The trochlear complex as seen in a series of human embryos and fetuses (4 mm. onward) is described. An account of the development of the isthmus rhombencephali is also included. The question how the trochlear nerve reaches the dorsal region of the brain stem is answered, and the nature of the decussation is described. The investigation has not revealed why the decussation occurs or why it takes place on the dorsal aspect of the brain stem. The trochlear nucleus originates in series with the oculomotor nucleus, but in the basal plate of the isthmus. As the lateral walls of the isthmus link the metencephalic alar to the mesencephalic basal plate, the basal plate of the isthmus becomes compressed until it assumes a position at the ventral extremity of the lateral wall of the isthmus, and it is here that the trochlear nucleus is situated at first. The fibers from the nucleus form a bundle, which turns dorsally at once and thus gains an alar situation in the lateral wall of the isthmus. The nerve then proceeds through the lateral wall of the isthmus caudally to the superior medullary velum, where the decussation occurs. The article is illustrated with unusually fine photographs.

W. ZENTMAYER.

Conjunctiva

OPERATIVE TECHNIC FOR POSTERIOR SYMBLEPHARON. E. ROMERO, Arch. Soc. oftal. hispano-am. **6**:1161 (Nov.) 1946.

The author, aware that recurrence after the present operative procedures for posterior symblepharon is common, used a simple method of his own in dealing with this condition in 3 cases. With this procedure, a posterior symblepharon is changed into an anterior one by passing through the posterior part of the adhesion a thick needle threaded with a bundle of threads, which are left loose like a drain. A few days later, after epitheliation of the tunnel has taken place, the remaining bridge of tissue is cut as though one were dealing with an anterior symblepharon. Good results were obtained in the 3 cases in which the method was used.

H. F. CARRASQUILLO.

SPONTANEOUS PROFUSE HEMORRHAGE FROM THE CONJUNCTIVA OF BOTH EYES IN AN INFANT TREATED WITH BLOOD TRANSFUSION. I. SANDUKOVSKY and Z. DEGGELLER, Vestnik oftal. **25**:35, 1946.

A hemorrhage from the conjunctiva of both eyes was present in an infant on the second day after birth. The lids were edematous, and there

was continuous bleeding with formation of clots of blood in the conjunctival sacs. The blood picture was that of anemia: 65 per cent hemoglobin, 3,290,000 red blood cells and poikilocytosis. A history of hemophilia could not be established.

A transfusion of 50 cc. of blood was given on the following day; the bleeding stopped in a few hours and did not recur.

OLGA SITCHEVSKA.

Cornea and Sclera

SCLERAL NECROSIS IN PERIARTERITIS NODOSA, F. HARBERT and S. D. MCPHERSON JR., Am. J. Ophth. **30**:727 (June) 1947.

Acute otitis media developed in a 31 year old man, as well as abscess of the nasal septum and apparently an allergic reaction to sulfonamide compounds. He recovered, with considerable saddleback deformity of the nose, dacryocystitis and deafness. Following dacryocystectomy, bilateral superficial punctate keratitis occurred. A subconjunctival hemorrhage developed in each eye above the upper limbus. The conjunctiva became edematous and ulcerated. The underlying sclera sloughed and the interior of the eyes became involved, and final vision was 1/200 in the right eye and 2/200 in the left eye. Sections from the gastrocnemius muscle showed changes consistent with periarteritis nodosa.

W. S. REESE.

SURGICAL TECHNIQUE OF CORNEAL TRANSPLANTATION IN RABBITS. F. C. STANSBURY and J. A. C. WADSWORTH, Am. J. Ophth. **30**:968 (Aug.) 1947.

Stansbury and Wadsworth described a satisfactory method of keratoplasty on rabbits following in general the technic of Castroviejo. They recount the difficulties and methods of solving them.

W. S. REESE.

ACTINIC KERATOCONJUNCTIVITIS. V. CHULIA, Arch. Soc. oftal. hispano-am. **6**:1253 (Dec.) 1946.

The author concludes that there is no doubt of the importance of the physical constitution of the individual patient in the causation of actinic keratoconjunctivitis. He has never seen the condition in robust people with dark skin. Lymphatism in all its aspects (pale, thin skin; sparse pigmentation; weakness; underweight) are etiologic factors of importance. The sun, by the action of its rays, gives rise to the disease, but the aforementioned constitutional factors must be present for its occurrence.

H. F. CARRASQUILLO.

Experimental Pathology

PRIMARY AND SECONDARY CHANGES IN THE EYE IN TULAREMIA. A. KRUTOVA, Vestnik oftal. **26**:23, 1946.

Krutova infected guinea pigs with tularemia by instilling 1 drop of pure culture of Bacillus tularensis into the conjunctival sac, or by inject-

ing the culture subconjunctivally; the other eye served as a control. Clinical changes similar to those in the human eye were observed on the fifth day of the experiment. The guinea pigs had a generalized infection and died on the third to the tenth day. The eyeballs, lids, internal organs and lymph nodes were examined under the microscope. The internal organs showed necrotic granulomatous foci. The conjunctiva showed necrosis and inflammatory infiltration. Specific granulomas were also found in the ciliary muscles, which was rather unusual. The control eye showed no changes.

The regional lymph nodes were not affected, as the guinea pigs died too soon from generalized infection; i.e., Parinaud's syndrome was absent.

Krutova described another infected guinea pig with generalized tularemia, in which secondary changes were observed in both eyes. There was no regional lymphadenitis. Episcleral necrosis appeared only on the eighth or ninth day.

Cutaneous changes of the lids and of the body were of the characteristic "rosette" form, similar to changes in the conjunctiva. These rosette changes in the skin, which appear on the eighth to the ninth day, and which may be called skin "granulomatosis," are secondary changes and are of hematogenous origin, or of the same origin as the secondary changes in the eye. The temperature flared up with the appearance of the cutaneous and ocular lesions.

Krutova believes that in a case of tularemia all organs should be carefully examined, as the spread of the disease might be extensive despite few subjective symptoms.

OLGA SITCHEVSKA.

General Diseases

THE NEW OCULOBUCCAL-GENITAL SYNDROME: REPORT OF A CASE WITH VERIFICATION OF ACID-FAST BACILLI AND PATHOLOGIC EXAMINATION. R. JEBEJIAN and B. KALFAYAN, Ann. d'ocul. **178**:335 (Aug.) 1945.

The authors report a case of the oculobuccal-genital syndrome which they have followed for nearly six years. The lesions are manifest chiefly on the mucous surfaces of the mouth, pharynx and genitals and in the eyes. The disease affects both sexes, and in the reported cases it has usually occurred in the second or the third decade of life. The three cardinal features may be present at the same time, or they may occur singly. The buccal lesions are most frequently aphthous ulcers. They are discrete and painful and disappear in a few days.

The genital lesions are also ulcerative. They occur on the scrotum or the vulvae. They may be single or multiple. They are painful and last anywhere from a few days to two weeks. The ocular lesion is most commonly a bilateral iritis, which is frequently accompanied with a hypopyon. Conjunctivitis, keratitis, uveitis, retinitis, neuroretinitis and optic neuritis may also occur.

The authors report the clinical course of their patient in detail. They describe the pathologic changes observed in one of the buccal ulcers which they excised. The most significant observation was the presence of an acid-fast bacillus, resembling the bacillus of avian tuberculosis. A general discussion of the reported cases is also presented. Adamentiades,

who reported the first case of this syndrome, expressed the belief that a staphylococcus was responsible for the lesions. Behcet, at a later date, suggested that the etiologic agent was probably a virus. Others have expressed the belief that the lesions are allergic. The authors hope to continue their investigations in other cases in order to verify their observation of an acid-fast bacillus.

P. Robb McDonald.

Photophobia Associated with Infantile Acrodynia. I. Esente, Riv. di oftal. **1**:392, 1946.

The author describes 5 cases of infantile acrodynia accompanied with photophobia. He presents a critical review of the more modern views on the pathogenesis and therapy of acrodynia and expresses favor toward the idea of a neurotropic factor or agent residing perhaps in the vegetative centers of the infundibulum and the tuber cinereum.

A contributing factor may be an avitaminosis, for relief of which various investigators prefer polyvitamin therapy, rich in the B factors.

The explanation of the photophobia on the basis of ocular hyperesthesia or a sympathetic state does not seem persuasive or adequate. The author feels that its origin lies either in a retinal hyperexcitability resulting from an altered local metabolism, and determined by the pathogenic agent operative in acrodynia, or in the absence of definite anatomic-physiologic connections between the diencephalon and the retina. He further believes that profound psychosomatic changes present in acrodynia by virtue of the disturbance in the higher vegetative centers may be responsible for the irritative state of the light sense, thus producing photophobia.

G. B. Bietti—J. J. Lo-Presti.

Cerebral Complications (Papilledema) in Epidemic Parotitis. H. O. Esbjerg, Acta ophth. **21**:119, 1944.

Two cases of papilledema as a sequel to epidemic parotitis are reported. The intracranial symptoms simulated those of a tumor in the roof of the fourth ventricle and are due to obstruction of the basal foramens caused by arachnoiditis.

O. P. Perkins.

Reiter's Disease. M. Zewi, Acta ophth. **25**:47, 1947.

The author gives brief histories of 10 cases that seem to correspond to the description of Reiter's disease. Seven of the 10 patients showed the characteristic triad of polyarthritis, conjunctivitis and urinary tract disturbance. Three patients showed only the joint and eye symptoms. The author can shed no light on the pathogenesis of this queer condition except to stress that it seems to be in some way associated with an intestinal infection.

O. P. Perkins.

Glaucoma

THE USE OF FURMETHIDE IN COMPARISON WITH PILOCARPINE AND ESERINE FOR THE TREATMENT OF GLAUCOMA. E. U. OWENS and A. C. WOODS, Am. J. Ophth. **30**:995 (Aug.) 1947.

Owens and Woods conclude that "furmethide" (furfuryl trimethylammonium iodide) is more effective than pilocarpine and physostigmine in the treatment of primary glaucoma in which the tension exceeds 40 mm. of mercury (Schiötz). It is also effective in certain cases of primary glaucoma in the lower tension groups in which treatment with pilocarpine has failed.

W. S. REESE.

ROLE OF HEREDITY IN GLAUCOMA. S. A. FIALHO, Rev. brasil de oftal. **5**:19 (Sept.) 1946.

Clinical observations show that heredity plays an important part in the genesis of glaucoma. Von Graefe called attention to the "rule of anticipation" which is observed in familial glaucoma, the disease appearing earlier in successive generations. Numerous authors have confirmed this observation. Attention has also been drawn to the frequent appearance of glaucoma, with other hereditary anomalies, such as retinitis pigmentosa and aniridia. Special mention is also made of the fact that hereditary glaucoma is often associated with myopia, statistics having shown that 50 per cent of the cases of juvenile glaucoma occur in myopic persons. Racial influence has also been admitted, the Jews and Negroes being particularly disposed to the disease. The author presents 2 interesting cases, in 1 of which the disease was transmitted from the father to 2 of his 6 children. In the other the disease has appeared in three successive generations and is manifest in the fourth. Both case histories confirm the "rule of anticipation."

M. E. ALVARO.

PERIPUPILLARY WEB OF VESSELS IN HEMORRHAGIC GLAUCOMA. E. HOLM, Acta ophth. **23**:343, 1945.

Ten cases are described. The author stresses peripupillary infection as an important diagnostic sign of hemorrhagic glaucoma. The vascularization consists of loops of vessels, forming a layer anterior to the pupillary sphincter. That such new-formed vessels occur in cases of old hemorrhagic glaucoma has long been known, but the author holds that they are present immediately after symptoms of glaucoma develop. Subsequently, the picture is altered by the ingrowth of vessels from the periphery of the iris.

Thiel thinks the vessels form in consequence of stasis due to increased tension.

The author regards arteriosclerotic lesions of the vessels, with obstruction of many uveal vessels, as a reasonable cause.

O. P. PERKINS.

Lacrimal Apparatus

CONTRIBUTION TO THE STUDY OF CONGENITAL FISTULA OF THE LACRIMAL SAC. M. TORTI, Ital. d'ottal. **13**:69, 1946.

After a brief review of the bibliography, the author reports 2 cases of congenital unilateral fistula of the lacrimal sac. From the histologic examination of the first case, in which numerous lymphocytes interspersed with mast cells and plasma cells were noted in the subepithelial connective tissue, an inflammatory origin was surely operative, while in the second case one was dealing with a congenital anomaly. According to the author, without a suitable histologic examination of sections of the tissues, one cannot make a diagnosis of congenital fistula even when the history dates back to earliest childhood and lacks inflammatory episodes. True congenital fistulas arise from the promotion of a supernumerary and aberrant lacrimal canal, developing in manner and time as do the normal lacrimal conaliculi.

G. B. BIETTI—J. J. LO-PRESTI.

MASSIVE POLYP OF THE LACRIMAL SAC CURED WITHOUT INTERVENTION. F. A. CHAVARRIA LOPEZ, Arch. Soc. oftal. hispano-am. **6**:1127 (Nov.) 1946.

The author differentiates between pseudopolyps occurring in a lacrimal sac the seat of a chronic inflammatory condition, which are merely sessile proliferations of the diseased mucous membrane, and true polyps, which are pedunculated growths with a definite histologic structure.

The case of a man aged 24 who had previously had acute dacryocystitis in both eyes at different times is reported. Later acute inflammation of the right lacrimal sac again developed. An abscess was formed, which opened spontaneously. Through the aperture a large, pedunculated true polyp herniated. The patient himself ruptured the polyp while applying compresses which had been prescribed.

H. F. CARRASQUILLO.

Lids

THE TREATMENT OF EPITHELIOMAS OF THE LIDS WITH RADIATION. (RADIUM AND ROENTGEN RAYS. MARC-ADRIEN DOLLFUS, Curie Foundation, 1946.

This 121 page supplement, read at the November 1946 session, must be perused in its entirety to realize the detailed study involved in this monumental work. The study began eight years ago in an effort to compare the surgical or diathermy coagulation approach with that of irradiation.

L. L. MAYER.

Neurology

DIVERGENCE EXCESS: AN ANOMALY OF THE EXTRAPYRAMIDAL SYSTEM. E. HEALY, Am. J. Ophth. **30**:753 (June) 1947.

Healy concludes that divergence excess is not correlated with refraction and that orthoptics is the most satisfactory treatment because it

corrects, to a great extent, the neurologic factor. He also concludes that divergence excess is an anomaly of the extrapyramidal system and that research in this field is urgently needed.

W. S. Reese.

Mesencephalic Parinaud's Paralysis. J. Verdaguer and M. L. Oliveras, Arch. chilena de oftal. **2**:226 (July-Oct.) 1946.

A man 33 years of age with a syphilitic history, complaining of almost constant occipital headache and vertigo, presented the following ocular symptoms: visual acuity was 5/10 in the right eye and 5/7.5 in the left eye. The pupils were normal; the photomotor reflex, however, was abolished, but the reaction in convergence and accommodation was preserved. The fundus was normal in both eyes. Moderate exotropia was present in the left eye.

In performing the voluntary ocular movements there was marked limitation of the upward excursions, and in an effort to turn the eyes straight up the upper lids were retracted and convergent and divergent movements were initiated, those of divergence predominating. On looking up and to the right and up and to the left, the eye in adduction moved to a higher level.

The reflex upward movements were also restricted, and Bell's phenomenon was absent. There was diplopia in looking up and to the right and up and to the left.

The visual fields showed slight bitemporal limitations and enlargement of both blindspots. Results of the clinical laboratory examination were essentially negative, except for an increase (4 Gm.) in the albumin content of the cerebrospinal fluid.

Roentengrams were suggestive of a cerebral tumor in the quadrigeminal region, showing destruction of the posterior clinoid processes and the dorsum sellae.

The authors make a complete analysis of the case, and since the patient showed partial paralysis of the associated movements of elevation and the automatic reflex movements (incomplete paralysis of convergence and Argyll Robertson pupils) he arrived at the diagnosis of Perinaud's syndrome. As to the etiology of the condition, he believes the causative factor to be an intracranial tumor located in the quadrigeminal region; this impression is sustained by the roentgenograms and the increased albumin content of the cerebrospinal fluid.

H. F. Carrasquillo.

Ocular Muscles

Divergent and Concomitant Strabismus. R. Arganaraz, Arch. de oftal. de Buenos Aires **21**:67 (April-June) 1946.

Argañaraz classifies strabismus as follows: 1. Divergent functional strabismus, usually noted at the end of the first period of infancy, although it may not appear until between the ages of 6 and 12 years. The stimulus to divergence, although weak, is permanent and thus tends to increase. This class of strabismus is difficult to treat surgically with success, as it is necessary to overcome the dynamic spasmodic action of

five of the six extraocular muscles. 2. Divergent strabismus due to amblyopia. When one eye ceases to function as a result of amblyopia, the retinal stimulus which keeps the eyes parallel is gradually lessened and the weak eye deviates outward for approximately 23 degrees. 3. Postoperative divergent strabismus. This type usually appears some time after tenotomy of the medial rectus muscle. It is noted in cases in which an extensive capsular débridement was carried out with the tenotomy or when the section of the medial rectus muscle was made 5 mm. or more from its scleral insertion. 4. Spasmodic divergent strabismus caused by the spasmodic contraction of the inferior oblique muscle, which rotates the eye outward and elevates the eyeball. The patient's head inclines toward the unaffected side; the head is carried forward until the chin touches the chest and is turned inward to compensate for the divergence. In the other eye the symptoms are exactly the reverse, owing to hypofunction of the superior rectus muscle. Tenotomy of the inferior oblique muscle is the only surgical procedure in cases of this type. 5. Paralytic strabismus (convergent and divergent). In a child, isolated paralysis of the medial rectus muscle is rare and when present causes a deviation of the eye outward. Paralysis of the lateral rectus muscle is much commoner and causes a strong convergent strabismus. These squints are easily recognizable, and they are noticeable from birth, the deviation often reaching 40 to 45 degrees. The author recommends tenotomy of the medial rectus muscle in cases of this type. Advancement and shortening of the lateral rectus muscles may also be performed. In cases of convergent strabismus controlled tenotomy and retroinsertion are recommended. Myectomy of the medial rectus muscle can also be associated with tenotomy of the lateral rectus. Surgical correction of postoperative divergent strabismus is difficult, and a muscle transplant is necessary. Tenotomy of the inferior oblique at its insertion on the lower orbital border is recommended in treatment of divergent strabismus in infants. A muscle transplant is the procedure of choice in treatment of paralytic strabismus, in order to replace the action of the paralyzed muscles. The article is accompanied with 20 illustrations.

M. E. Alvaro.

Operations

Present Evaluation of the Merits of the Z-Plastic Operation. John S. Davis, Plastic & Reconstruct. Surg. **1**:26 (July) 1946.

Denonvilliers is credited with creating the Z plastic operation in 1856. He made an incision shaped like a Z and transposed the two triangular flaps, obtaining relaxation and extension of tissue to correct ectropion. Morestin was the first to use multiple Z incisions in series. The mathematical basis worked out by Limberg gave the surgeon accurate information on how long the arms of the Z should be and on the best size of the angles formed by these arms.

A 60 degree angle of the arms of the Z is preferred, but the angle can be as acute as 20 degrees. The angles must be equal. When the incisions are made, two broad-based triangular flaps are formed whose bases are opposite each other. They are transposed and sutured without tension, forming another Z, turned approximately 90 degrees. The amount of the extension of the tissues will be the difference between the lengths of

the long and short diagonals of the parallelogram made by projecting lines across the bases of the triangles marked out by the Z, the short diagonal being the central line of the Z and the long diagonal being the distance between the distal ends of the arm lines.

Davis recommends the procedure for relaxation of scar tissue and prefers it for this to skin grafting or transplanting flaps from a distant part. It is simpler than most methods and utilizes tissue that otherwise would be discarded.

L. P. GUY.

Orbit, Eyeball and Accessory Sinuses

EFFECT OF ELECTRIC STIMULATION ON OCULAR TENSION. P. B. ZARETSKAYA, Am. J. Ophth. **30**:589 (May) 1947.

Zaretskaya found that positive galvanism reduced ocular tension but that there was no such constancy from negative galvanism.

W. S. REESE.

PROGRESSIVE EXOPHTHALMOS. T. BARDRAM, Acta ophth. **22**:1, 1944.

The literature dealing with advanced progressive exophthalmos is surveyed. Three cases are reported, in all of which an increased output of gonadotropic hormone occurred in the urine. In 1 case the basal metabolism was increased, although there were no other signs of thyrotoxicosis. The pathogenesis of this condition is discussed and is believed by the author to lie in a disturbance of hormone correlation arising from removal of the thyroid gland.

O. P. PERKINS.

ORBITAL COMPLICATIONS FOLLOWING OPERATIONS ON PARANASAL SINUSES. E. GOLDTFREDSEN, Acta ophth. **22**:401, 1944.

From a survey of case reports since 1902 and from a study of 8 cases of his own, the author concludes that orbital complications after operations on the frontal and maxillary sinuses are rare. They usually take the form of transitory orbital edema or paralysis of a solitary extraocular muscle. The complications following operations on ethmoid cells are severer and more frequent, taking the form of lesions of the optic nerve or orbital hematoma.

O. P. PERKINS.

Retina and Optic Nerve

MODIFICATIONS OF THE FORMULA OF BLOOD IN THROMBOSIS OF THE CENTRAL RETINAL VEIN. THOMAS, CORDIER, PIERQUIN and HENRY, Bull. Soc. d'opht. de Paris, (Nov.-Dec.) 1946, p. 72.

The authors divide cases of thrombosis of the central vein into three types: those occurring in youth, in which an inflammatory origin is usual; those in which syphilis or tuberculosis is the etiologic factor, and those due to foci of infection. Basically, in the majority of cases in all three types there is angiosclerosis and often hypertension. Increase in

platelet count and also increase of red blood cell count are frequent findings. Treatment by roentgen therapy to reduce platelets and number of red blood cells may prevent further accidents. The use of dicumarol is not without danger.

L. MAYER.

MINIMAL RETINAL ARTERIAL HYPOTENSION IN FATAL BARBITURATE INTOXICATIONS. C. HENRY, Bull. Soc. d'opht. de Paris, (Nov.-Dec.) 1946, p. 76.

Henry reports on 3 patients who died from an overdose of barbiturates in which it was possible to measure the retinal arterial tension. Diagnostically, a low arterial tension may be an earlier sign in these cases than loss of the swallowing reflex. In all patients with coma such a measurement is indicated, and if found to be very low is strongly suggestive of barbiturate poisoning.

L. MAYER.

PATHOGENESIS AND TREATMENT OF RETINAL DETACHMENT OF TUBERCULOUS ORIGIN. A. POKROWSKY, Vestnik oftal. **25**:17, 1946.

A review of the literature indicates that retinal detachment in tuberculosis of the eye is caused by changes in the retinal vessels: perivasculitis, hemorrhages and retinitis proliferan. Some authors believe that the changes in the vessel wall are caused (Lotin) not only by toxins but also by the tubercle bacilli.

Pokrowsky believes that prolonged tuberculosis of the choroid disturbs the nutrition of the retina and produces its degeneration in a broad sense, including degeneration of the vitreous. Although tuberculous detachment is of the exudative type and does not present a tear, slight trauma may lead to tear in the diseased retina. A history of such a case is given in detail.

The conclusions are as follows: 1. Retinal detachment with a tear may form in tuberculous chorioretinitis due to a slight, indirect trauma, and appear as a primary idiopathic detachment. A careful history, ophthalmoscopic and general examination will reveal the tuberculous origin of the detachment.

2. The presence of the tear in the detachment is an indication for a diathermy operation.

3. The positive results of the operation should not divert the attention of the ophthalmologist, and the specific tuberculous treatment should be continued.

4. In each detachment of the retina, the tuberculous causation should be kept in mind.

OLGA SITCHEVSKA.

ON THE DEPTH OF CAUTERIZATION IN SURFACE DIATHERMY, WITH SPECIAL REFERENCE TO DETACHMENT OPERATIONS. B. ROSENGREN, Acta ophth. **24**:389, 1946.

The following excerpt is from the author's summary: A correctly balanced surface action is of importance in detachment operations done by

means of surface diathermy on the sclera. On the basis of his own observations, which indicated that effects of excessive strength could be obtained with electrodes of the size commonly employed, the author has made an experimental study of the depth of cauterization under different conditions. Cattle livers were used as test material. The results show that the depth of the effect is conditioned by these factors:

1. The depth of the effect is increased when the water content of the surface is high.

2. The depth of the effect is greater when diathermic cauterization is performed with a weak current for a relatively long period than when a strong current is allowed to act for a short time.

3. The larger the electrode, the deeper is the effect. If the degree of moisture on the surface and the time of coagulation are standardized, it is possible to regulate the depth of the effect quite accurately by using different electrodes. Visual judgment of the coagulation process appear to permit a relatively high degree of accuracy.

O. P. PERKINS.

Tumors

LYMPHANGIOENDOTHELIOMA OF THE ORBIT SIMULATING A LACRIMAL GLAND. M. VERZELLA, Riv. di oftal. **1**:343, 1946.

The author describes a case of lymphangioendothelioma of the orbit. The clinical picture, that of a neoplasm developing in the region of the lacrimal gland, led one to suspect at first a tumor of the gland itself. Histologic examination pointed to the exact diagnosis of the origin and nature of the neoplasm. Excision of the tumor was followed by rapid healing, without recurrence in more than two years.

G. B. BIETTI—J. J. LO-PRESTI.

ANGIOMA OF THE CHOROID. G. CRISTINI, Riv. di oftal. **1**:374, 1946.

The author emphasizes the rarity of choroidal angioma and reports a case under his observation. He refers to clinical features which, within certain limits, can serve as diagnostic signs. He states that these are of congenital origin and that, according to the concept of di Marzio with regard to orbital angiomas, there is operative an initiative stimulus brought on by the changes in the circulation in the affected part.

The author discusses some features of the histogenesis of the choroid on the basis of his own observations on the histopathologic features of his case.

G. B. BIETTI—J. J. LO-PRESTI.

TYPES AND VARIANTS OF EPIBULBAR EPITHELIOMAS: A TYPICAL INVADING AND CACHEXIA-PRODUCING EPITHELIOMA AND A BARELY MALIGNANT EPITHELIOMA ARISING FROM THE KERATOCONJUNCTIVA (TYLOMA). M. VERZELLA, Riv. di oftal. **1**:909, 1946.

The author describes 2 cases of epibulbar epithelioma, interesting because of the anatomicoclinical characteristics which distinguish them from the cases reported in the literature to date.

The first case was characterized by the extreme malignancy of the neoplasm. Three months after its excision, it recurred so rapidly that within a month it invaded almost the entire surface of the globe, the periorbital tissue, the ciliary body and the suprachoroidal space, perforated the globe in two places (at the limbus and the ora serrata) and metastasized to the regional lymph nodes and the internal organs, producing rapid cachexia and, finally, the death of the patient. The second case was one of an intermediate or a typical epithelioma with a benign clinical course, corresponding to that of a conjuctival tyloma.

The author presents the possibility that epitheliomas may arise from a preexisting tylomatous change, which, while not always innocuous because of the degenerative changes in the cornea it may cause, has a certain predisposition to develop into cancer.

The great shrinkage of the lesion with roentgen rays, diathermy or high frequency waves is the therapeutic test.

G. B. Bietti—J. J. Lo-Presti.

Retinoblastoma in a Man Aged 48 Years. K. Rasmussen, Acta ophth. **21**:210, 1944.

A blind, irritable eye was removed from a man aged 48. Histologic examination revealed the presence of a retinoblastoma.

O. P. Perkins.

A Case of Reticulum Cell Sarcoma of the Plica Semilunaris. K. van Walbeek, Acta ophth. **24**:183, 1946.

A man aged 58 had a reticulum cell sarcoma of the plica semilunaris. He died two years later of metastases of the skull. A summary of the literature on this condition is given.

O. P. Perkins.

Uvea

Angioid Streaks. B. A. Klien, Am. J. Ophth. **30**:995 (Aug.) 1947.

Klien reports 6 cases of angioid streaks, including the histologic changes in two eyes. She concludes that the condition is based on abnormal fragility and opacification of the lamina basalis of the choroid. Previous studies have revealed that degeneration of the elastic portion of this membrane is the initiating factor, this corresponding to a general inferiority of the elastic tissue of the body as indicated by the frequent association with pseudoxanthoma elasticum and with severe degenerative vascular disease.

W. S. Reese.

Vision

Twilight Vision and Vitamin A. T. Angios, Rassegna ital. d'ottal. **13**:11, 1946.

Angios has sought to improve twilight vision beyond the limits usually obtained after adaptation by administering vitamin A to normal per-

sons without vitamin deficiency. Previous experiments by other writers have yielded results which disagree with those of the author. Examinations were conducted on 51 persons of the same age without general or ocular defects and leading the same type of life. They were divided into three groups: The first worked strenuously for forty minutes on the telemeter daily; the second also worked daily for thirty minutes at a forced pace; the third carried on normal activities without special exertion. To avoid errors due to undeterminable factors, each group was subdivided into three subgroups, of which the first served as a control and the second and third as subjects for the experiment. The determinations were made in a room illuminated by reduced daylight admitted through the crack of a closed window. The constancy of the light was checked by a Leica light meter, observations being made only when the intensity was constant. Visual acuity was measured by Landolt rings after a forty minute adaptation. After a series of determinations showing constant results, 50,000 international units of vitamin A was administered to the second subgroup, and 100,000 vitamin A units to the third subgroup. Observations were repeated as before. The author shows by a series of tables and graphs that an improvement of twilight vision was obtained after administration of vitamin A, more evident when a dose of 10,000 international units was used, and specially in persons working at a forced pace. He ends by advising administration of vitamin A to all who must exhaust their threshold capacity, especially if it tends to lessen from fatigue or from long exposure to intense light.

G. B. Bietti—J. J. Lo-Presti.

Vitreous

The Substitution of Cerebrospinal Fluid for Vitreous Clouded with Opacities. M. H. Fritz, Am. J. Ophth. **30**:979 (Aug.) 1947.

Fritz reports 4 patients in whom cerebrospinal fluid was substituted for cloudy vitreous. The vision of the youngest was improved from light projection to 20/20-1. He had had a vitreous hemorrhage a year previously from an ocular contusion.

W. S. Reese.

Sympathetic Ophthalmia

On Meningeal Reactions in Sympathetic Ophthalmitis. L. Corcelle, Brit. J. Ophth. **31**:366 (June) 1947.

Three cases of sympathetic ophthalmitis are reported in which meningeal reactions were noted. In 2 of the cases the microscopic examination of the enucleated eye is stated to have shown the "inoculation chancre" described by Redslob. No histologic report is given in the third case.

The time of onset of lymphocytic meningitis is indicated by lumbar puncture, which may perhaps be regarded as contemporaneous with the appearance of clinical signs in the sympathizing eye.

W. Zentmayer.

A NEW SYMPTOM IN SYMPATHETIC OPHTHALMIA. L. GUGLIANETTI, Rassegna ital. d'ottal. **13**:5, 1946.

Anatomic and pathologic studies of sympathetic ophthalmia have shown that in the initial stages of the disease the inflammatory process of the uvea is particularly pronounced in the posterior part, gradually diminishing in intensity anteriorly toward the ciliary body and posteriorly toward the macula.

The author has sought to demonstrate a diminution in the sensitivity of the retina in the zone under discussion (between the macula and the periphery) by means of campimetry.

In 3 cases of sympathetic ophthalmia he has demonstrated a ring scotoma, which was present only when the surrounding illumination was dim. The Maggiore perimeter, with targets of low intensity, served the purpose best.

The diminution in the light sense in the form of a ring scotoma is a new sign of early sympathetic ophthalmia.

G. B. BIETTI—J. J. LO-PRESTI.

SYMPATHETIC OPHTHALMIA FOLLOWING SUBCONJUCTIVAL RUPTURE OF THE SCLERA. C. E. LUGUE, Arch. chilenos de oftal., **2**:26 (Nov.-Dec.) 1946

A man aged 33 was examined three days after a blow was received on the right eye. A subconjunctival rupture of the sclera in the superoexternal region was present. There was no hernia of the uvea or any superficial symptom which might suggest subconjunctival dislocation of the globe. A total hyphema prevented examination of the fundus. Vision was reduced to light perception. The ocular tension was low. Nine days later the patient was discharged. Two months later the right eye was blind, and the vision in the left eye was reduced to perception of hand movements. A diagnosis of sympathetic ophthalmia was made. The author points out that this complication is rare in cases of scleral rupture. Enucleation was not deemed advisable, and the usual treatment was given. The patient died of acute hepatic insufficiency, and it was impossible to obtain the eye for pathologic examination.

M. E. ALVARO.

Therapeutics

SODIUM SULFACETIMIDE. W. L. BENEDICT and J. W. HENDERSON, Am. J. Ophth. **30**:984 (Aug.) 1947.

Benedict and Henderson found sodium sulfacetimide in a 30 per cent solution or a 10 per cent ointment safe for average clinical use. The solution gave better results, and the drug was more efficacious in acute varieties of catarrhal and purulent conjunctivitis.

W. S. REESE.

EXPERIMENTAL AND CLINICAL STUDY OF THE ANTISEPTIC ACTION OF MERBROMIN ["MERCUROCHROME"]. M. MAIONE, Ann. di ottal. e clin. ocul. **72**:114, 1946.

The author has begun a series of studies in vitro and in vivo to investigate the value of merbromin ("mercurochrome") in ophthalmic practice. The results obtained showed that the drug is active against the conjunctival flora and is effective in septic diseases of the globe and the adnexa.

G. B. BIETTI—J. J. LO-PRESTI.

PENICILLIN IN OPHTHALMOLOGY. S. BERRENCHEA and R. CONTARDO, Arch. chilena de oftal. **4**:12 (Jan.-Feb.) 1945.

After discussing the value of penicillin in treatment of various ocular diseases, the author summarizes the results in 32 cases, distributed as follows: chronic blepharitis, 8 cases; bacterial conjunctivitis, 16 cases; serpiginous corneal ulcer, 3 cases; perforating wounds of the cornea, 2 cases; panophthalmitis, 2 cases, and iritis, 1 case. In every case the results were splendid. The local method of treatment is indicated with diseases of the lids, the lacrimal passages, the conjunctiva and the cornea. With diseases of the iris, systemic administration is preferred. For action on the aqueous humor, local treatment should be combined with subconjunctival injections or injections into the anterior chamber together with systemic treatment. With conditions of the vitreous, injections into this body should be added.

H. F. CARRASQUILLO.

VITAMIN P IN OPHTHALMOLOGY. P. MATA, Arch. Soc. oftal. hispano-am. **6**:1257 (Dec.) 1946.

Vitamin P is a complementary factor of vitamin C. In 1936 Szent-Györgyi and his associates proved that concentrated vitamin C obtained from lemons and oranges had some action on the pathologically increased permeability of the capillaries, whereas pure or synthetic ascorbic acid had no action whatever. They succeeded in isolating a crystalline substance, which they called citrin. This substance acted on the excessive permeability of the capillaries, and because of this action it was called vitamin P. In spite of its crystalline structure, it is not a simple substance, but an isomorphous mixture of its two component glucosides, hesperidin and eriodictyol.

Like vitamin K, its use is indicated in types of hemorrhages produced by hypothrombinemia. Scurvy, infections and anaphylactic vascular purpuras were first treated with this vitamin. For its therapeutic use, the hemorrhage need not be due to a hypovitaminosis of any kind. Clinically, the beneficial effect of vitamin P has been proved in hemorrhages of uncertain origin. Thus, combined with treatment for the causative factor, its use is of value in focal iritis with hyphema, hemorrhages occurring in certain forms of severe iridocyclitis and diabetic iritis with rubeosis iridans.

The value of vitamin P also has been proved in the treatment of eczematous conditions of the lids accompanied with conjunctivitis and of

keratitis of scrofulous origin. Through its action on the permeability of capillaries, this vitamin has shown a beneficial effect on hemorrhagic retinopathies of nephritic origin. In cases of extensive retinal hemorrhages, subchoroidal extravasations and thrombosis of the central vein, it may be advantageously used. It may also be used in cases of juvenile recurrent hemorrhages of the vitreous.

The author has been in the habit of giving vitamin P combined with ascorbic acid as a prophylactic measure before surgical operations.

H. F. CARRASQUILLO.

USE OF VITAMIN K IN TREATMENT OF INTRAOCULAR HEMORRHAGES. N. AZAROVA, Vestnik oftal. **25**:2, 1946.

Azarova observed 32 patients with intraocular hemorrhages of various cases. Fifteen patients had tuberculous choroiditis; of these, 4 patients had juvenile recurrent hemorrhages into the vitreous. Seven patients were elderly persons with hypertension and fragility of the vascular walls, and 10 patients received a preparation of vitamin K as a prophylactic measure before operative procedures.

The best results were obtained in the cases in which vitamin K was used before operations or in elderly patients with hypertension and fragility of the vascular walls. The patients with juvenile recurrent hemorrhages into the vitreous were not benefited by the vitamin K treatment; nor were the patients with tuberculous choroiditis. It is best to give vitamin K for only three days, as there was noted an increase of bleeding in some cases when the vitamin was given for ten days.

OLGA SITCHEVSKA.

Toxic Amblyopia

ALTERATIONS OF THE VISUAL FIELDS IN TOBACCO AMBLYOPIA. L. HANBRESIN and C. SCHEPENS, Bull. Soc. d'opht. de Paris, Nov.-Dec. 1946, p. 79.

The authors found that 0.4 per cent of the patients brought into their clinic in occupied Germany had tobacco amblyopia. The central field as registered on the Bjerrum screen covered 30 degrees from fixation. The scotoma was for most cases central but often a cecocentral scotoma was noted. In severe cases a depression of the entire visual field with greatest encroachment in the superior temporal field was noted. The scotoma usually may be shown to follow the anatomic distribution of the papulomacular nerve fiber bundle.

L. MAYER.

Book Reviews

La neuro-angiomatose encephalo-faciale. By A. M. Larmande. Price, 400 francs. Pp. 150. Paris: Masson & Cie, 1948.

This is a monograph on the condition commonly known in this country as the Sturge-Weber syndrome. A historical review of the subject is followed by the author's own observations on the syndrome as it is met with clinically. This is followed by a section on the theory of the physiopathology of the disease and its treatment. The volume is probably the most important monograph on the Sturge-Weber syndrome that has appeared.

FRANCIS HEED ADLER.

Management of Binocular Imbalance. By Emanuel Krimsky, M.D. Pp. 464, with 200 illustrations. Philadelphia: Lea & Febiger, 1948.

While the title suggests that this book deals with the heterophorias exclusively, it is concerned equally with the manifest, as well as the latent, deviations. For many years, the author has advocated a unique approach to the study of oculomotor disturbances. He believes that since the corneal light reflex is the most important objective landmark, the deviations of this reflex should be noted rather than the movements of the eye. All the observable phenomena are therefore presented from this point of view. While this thesis is supported by many good arguments, it is apt to be confusing at first to one accustomed to observe movements of the eye rather than movements of the light reflex, which obviously are in the opposite direction. This is a minor point, however, and not a justifiable criticism in view of the excellent illustrations. These are diagrammatic and for the most part have been drawn by the author. They are superb and do what an illustration is intended to do, i.e., make the text clear at a glance.

The first chapter is taken up with a consideration of the corneal light reflex. The next five chapters consider the anatomy and physiology of the ocular muscles. Chapter 6, dealing with the heterophorias, is especially commendable, since the author approaches this subject from the physiologic aspect. Chapter 7 deals with prisms, particularly the aspect of the effect of prisms on the corneal reflex. Chapter 9 is concerned with normal and abnormal binocular vision. The phenomena of normal and anomalous correspondence have been confused by so many writers, because of a wide variety of meanings in the use of certain terms, that most readers, like the reviewer, look hopefully into each new book on ocular muscles with the expectation of being enlightened. Unfortunately, the section on the corneal light reflex in retinal correspondence leads only to further confusion. Chapters 10, 11 and 12 are concerned with the examination of patients with binocular imbalance. Chapter 13, entitled "Neurological Considerations," deals with supernuclear and infranuclear ocular muscle palsies. Chapter 14 discusses the problem of squint in children. This chapter does not add anything to what is already known. In chapter 15 a number of miscellaneous topics are considered, such as occlusion, face

rotation and head rotation, visual skill in aviation and in industry, and ptosis. The last three chapters deal with the use of prisms, the stereoscope and surgical measures in treatment.

Taken as a whole, the book is useful in collecting this author's many contributions to the literature of squint, since nearly all of these are original in their point of view and many of them extremely valuable. While the reviewer would not advocate this book as a text for the student beginning his training, the experienced worker would find it worth while to review the whole subject of squint, using this book to obtain an entirely different point of view.

FRANCIS HEED ADLER.

Psychodynamics and the Allergic Patient. By Harold A. Abramson, M.D. Price not stated. Pp. 81, with 2 illustrations. Minneapolis: The Bruce Publishing Company, 1948.

The object of this book is to focus the attention of clinicians on the importance of emotional factors in the routine therapy of allergic conditions. The book is the outcome of a symposium, bringing together authorities in the field of psychiatry and allergy. It will be of particular interest to the ophthalmologist who has to treat allergic conditions.

FRANCIS HEED ADLER.

News and Notes

EDITED BY DR. W. L. BENEDICT

SOCIETY NEWS

Annual Meeting of Oregon Academy of Ophthalmology and Otolaryngology.—The tenth annual spring postgraduate convention of the Oregon Academy of Ophthalmology and Otolaryngology will be held in Portland, June 19 to 24, 1949. Another fine program has been arranged by the Oregon Academy and the University of Oregon Medical School. There will be four guest speakers—men outstanding in their respective fields: Dr. Lawrence R. Boies, professor of otolaryngology at the University of Minnesota Medical School, Minneapolis; Dr. Leland Hunnicutt, associate clinical professor of otolaryngology at the University of Southern California School of Medicine, Los Angeles; Dr. James H. Allen, professor of ophthalmology at the State University of Iowa School of Medicine, Iowa City, and Dr. Edmund B. Spaeth, professor of ophthalmology at the University of Pennsylvania Graduate School of Medicine, Philadelphia.

There will be lectures, clinical demonstrations and ward rounds.

Preliminary programs will be out about May 1. They may be secured, with further information, from Dr. David D. DeWeese, secretary, 1216 S.W. Yamhill Street, Portland 5.

In order that the course may be made more personal and practical, registrations will be limited to 125.